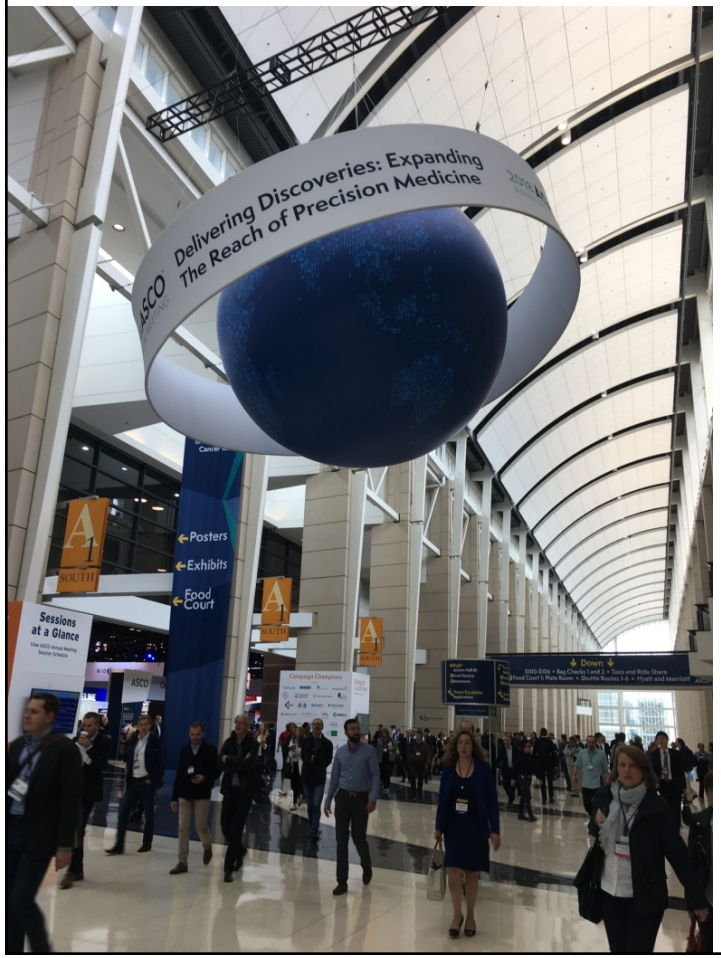
post-ASCO
Chicago June 1-4,2018

Sarcomi ossei pediatrici

Firenze 12dicembre2018



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ASCO Daily News

2018 ASCO ANNUAL MEETING

PEDIATRICS

Maintenance Therapy Improves Outcomes in Rhabdomyosarcoma

JUNE 4, 2018

Adding 6 months of low-dose maintenance

Pediatric Bone Sarcoma – Highlights

EWING SARCOMA

TEMIRI + VDC + IE in prima linea Meyers et al (USA)
Lurbinectedin Subbiah et al (intern)
Ewing pediatric vs adult Schwarts et al (USA)

OSTEOSARCOMA

Regobone *Duffaud et al (Fra)*
Lenvatinib in combinazione Gaspar et al (inter.)
Apatinib Xie et al (China)
Pazopanib + topotecan Agulnik et al (USA)
PAZIT Kiehoua et al (USA)
Drug repurposing Bouche et al (Belgium)

Ewing Sarcoma

Presentato anche CTOS2018

Memorial Sloan Kettering Cancer Center

The Addition of Cycles of Irinotecan/Temozolomide to Cycles of Vincristine/Doxorubicin/Cyclophosphamide and Ifosfamide/Etoposide For the Treatment of Ewing Sarcoma

Abstract 10533

Emily K Slotkin, Srikanth R Ambati, Manjusha Namuduri, Filemon Dela Cruz, Leonard H Wexler, **Paul A Meyers**

BACKGROUND

Effective therapy for Ewing sarcoma requires the combination of systemic therapy and local control of all sites of macroscopic disease. In North America, systemic therapy for Ewing sarcoma has evolved to include treatment with cycles of cyclophosphamide, doxorubicin, and vincristine (VDC) and cycles of ifosfamide and etoposide (IE). Improved outcome has been shown with dose intensification. Increasing dose intensification by shortening the intervals between cycles of chemotherapy (interval dose compression) was shown to improve outcome in a prospective randomized trial.[1] Increasing dose intensity of alkylating agents was associated with improved event free and overall survival (EFS and OS) in a trial at the Memorial Sloan Kettering Cancer Center (MSKCC)[2]. The Children's Oncology Group performed a randomized comparison of increased dose intensity alkylating agents and standard dose alkylating agents, and did not observe improved outcome, but this study did not maintain high dose alkylating agent therapy throughout treatment in the manner employed in the MSKCC trial.[3]

TABLE 1: **Chemotherapy dose intensification: Planned doses in mg/week**

Protocol	COG 7924[3]		AEWS 0031[1]		MSKCC P6[2]
Planned protocol duration	Standard 48 weeks	Intensified 30 weeks	Standard Q3weeks 42 weeks	Intensified Q2weeks 28 weeks	Q3weeks 21 weeks
Doxorubicin	7.8	12.5	8.9	13.4	14.3
Cyclophosphamide	225	366	200	300	800
Ifosfamide	1500	2400	1500	2250	2000
5 year EFS	72%	70%	65%	73%	82%

Several regimens have been employed as retrieval therapy for patients with Ewing sarcoma who relapse after frontline treatment with cycles of VDC and IE including irinotecan + temozolomide (i/T), topotecan + cyclophosphamide, and gemcitabine + docetaxel, among others. Pre-clinical testing of the combination of irinotecan and temozolomide at the St. Jude Children's Research Hospital (SJCRH) demonstrated an advantage of a protracted administration schedule of low dose irinotecan given over 5 days in two consecutive weeks with temozolomide administered daily during the first week in combination with irinotecan.[4]

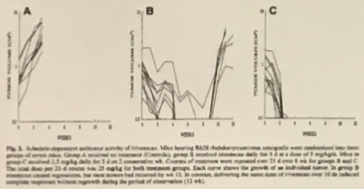

Fig. 3. Schedule-dependent antitumor activity of irinotecan. Mice bearing Rh28 rhabdomyosarcoma xenografts were randomized into three groups of seven mice. Group A received no treatment (Controls), group B received irinotecan daily for 5 d at a dose of 3 mg/kg/d. Mice in group C received 12.5 mg/kg daily for 5 d on 2 consecutive wk. Courses of treatment were repeated over 21 d once 8 wk for groups B and C. The total dose per 21-d course was 15 mg/kg for both treatment groups. Each curve shows the growth of an individual tumor. In group B monotoxic caused regression, but most tumors had recurred by wk 13. In contrast, delivering the same dose of irinotecan over 10 dc induced complete regression without regrowth during the period of observation (12 wk).

Clinical experience with i/T at recurrence is associated with substantial rates of response:

Table 2: **Clinical experience with i/T for recurrent Ewing sarcoma**

Author	Year	Patient #	CR	PR	MR	SD
Wagner[5]	2007	16	1	3	3	
Casey[6]	2009	19	5	7		
Raciborska[7]	2013	22	5	7		3

We postulated that the addition of cycles of i/T to cycles of VDC and IE might improve EFS and OS for newly diagnosed patients with Ewing sarcoma.

METHODS

We designed a prospective trial for the treatment of newly diagnosed patients with Ewing sarcoma. Patients were stratified by the absence (localized) or presence (metastatic) of clinically detectable metastatic disease at initial presentation. For patients with localized ES we administer high dose alkylator therapy with 4 cycles of VDC and 3 cycles of IE, followed by 6 cycles of i/T. For patients who present with metastases we intercalate 10 cycles of i/T with the same 7 cycles of high dose alkylating agent therapy.

TABLE 3: Treatment Regimens

Cycle	Localized Stratum	Metastatic Stratum
1	VDC	VDC
2	VDC	VDC
3	VDC	VDC
Local control		
4	IE	i/T
5	IE	i/T
6	IE	IE
7	VDC	i/T
8	VT	i/T
9	VT	IE
10	VT	i/T
11	VT	i/T
12	VT	IE
13	VT	i/T
14		i/T
15		VDC
16		i/T
17		VT

VDC:	**Cyclophosphamide 2.1 g/m²/day x 2 days Doxorubicin 37.5 mg/m²/day x 2 days Vincristine 2 mg/m²/day x 1 day**
IE:	**Ifosfamide 2.8 g/m²/day x 5 days Etoposide 100 mg/m²/day x 5 days**
i/T:	**Irinotecan 20 mg/m²/day x 5 days x 2 weeks (10 total doses) Temozolomide 100 mg/m²/day x 5 days**

RESULTS

We have enrolled 38 (22 patients=localized and 16 patients=metastatic) patients with ES. Patients enrolled on the localized stratum ranged in age from 5 to 22 (median 15); there were 18 patients with a bone primary and 4 patients with soft tissue primary (Table 4). Patients on the metastatic stratum ranged in age from 7 to 34 (median 17) (Table 5). With a median follow-up of 16 (5-52) months, patients with localized ES have achieved a 3 year EFS of 95% and overall survival (OS) of 95% (figures 1 and 2). With a median follow-up of 21 (2-52) months, patients with metastatic ES have achieved a 3 year EFS of 50% and OS of 70% (figures 3 and 4). Patients with metastatic disease limited to the lungs have a 3 year EFS and OS of 85%. (figure 5)

TABLE 4: Patient Demographics Localized Stratum

Age at Entry	Primary Site
10	T11-T12 region
11	9th rib
12	L fibula
13	L humerus
13	R thigh
14	R calf
14	R humerus
15	R femur
15	R fibula
15	T10
16	L1-L3
17	T1-T3 region
17	Posterolateral abdominal wall
17	L fibula
20	T11 vertebra
20	L cheeck/zygoma
21	L femur
22	L calf
5 yo	T7 vertebra
7 yo	L femur
8 yo	L humerus
8 yo	L femur (femoral neck)

22 patients
Age 5-22 (median 15)
Primary site:
Bone: spine 6, femur 4, humerus 3, fibula 3, chest wall 1
Soft tissue: extremity 2, retroperitoneum 1, face 1

TABLE 5: Patient Demographics Metastatic Stratum

Age at Entry	Primary Site	Additional sites
12	L Scapula	Vertebral bodies, bilateral iliac bones, sternum and right ischium
14	R Ischium	Pulmonary nodules
15	L post chest wall/rib	Bilateral parenchymal pulmonary nodules
16	Perineum	Appendicular and axial skeleton, skull, bilateral pulmonary nodules and BM
16	R Ilium	Pulmonary nodules
16	L 4th rib	Pulmonary nodules
17	R 7th rib	Pulmonary nodules, pleural nodes, L retrocural node, and a node above the L adrenal gland
17	L Pelvis	Pulmonary nodules
18	L Kidney	Vertebral bodies, thoracolumbar spine, pelvic bones, sternum, and pulmonary nodules
19	unclear	L3, manubrium, BM
20	L Kidney	Pulmonary nodules
21	Pelvis	Distant bone (humerus)
22	L Thigh	Pulmonary nodules
23	R Metatarsal bone	Pulmonary nodules
28	R Ilium	Bilateral pulmonary nodules and thoracic nodes
34	L Iliac wing	Sacroiliac joint, vertebral bodies, femoral head, pulmonary nodules, and brain (L skull base/temporal region)
7	R pubic ramus	Pulmonary nodules, distant bone

17 patients
Age 7-34 (median 17)
Primary site: pelvis 7, chest wall 3, kidney 2, perineum 1, scapula 1, metatarsal 1, multiple bones 1
Metastatic sites: pulmonary parenchymal nodules 8, lung and nodes 2, multiple bones +/- bone marrow 7

RESULTS (cont)

Figure 1: EFS for patients in the localized stratum

Figure 2: OS for patients in the localized stratum

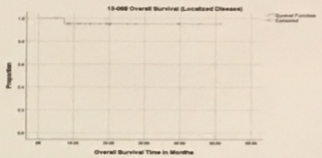

Figure 3: EFS for patients in the metastatic stratum

Figure 4: OS for patients in the metastatic stratum

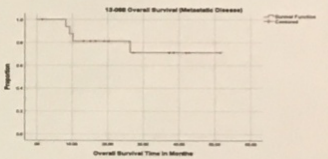

Figure 5: EFS for patients in the metastatic stratum with lung only metastasis

Figure 6: % Change in Tumor Size in Target Lesions after 3 cycles of VDC

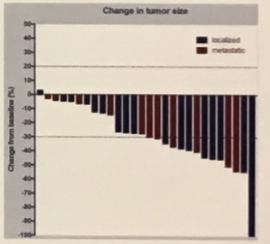

TABLE 6: Grade 3 and 4 Adverse Events

	Localized Stratum (total of 263 cycles)				Metastatic Stratum (total of 224 cycles)			
	Grade 3 (n, %)		Grade 4 (n, %)		Grade 3 (n, %)		Grade 4 (n, %)	
Febrile neutropenia	83	31.3%			18	7.9%	1	0.4%
Acute kidney injury	1	0.4%			2	1.9%		
Mucositis oral	1	0.4%			2	0.9%		
Typhlitis	1	0.4%				0.0%		
Nausea	3	1.1%			7	3.1%		
Vomiting	1	0.4%			5	2.2%		
Diarrhea					6	2.7%	1	0.4%
Dehydration	1	0.4%			2	0.9%		
Hypotension	1	0.4%			2	0.9%		
Catheter related infection	1	0.4%			2	0.9%		
Mucocutaneous herpes zoster	1	0.4%						
C diff colitis					2	0.9%		
Prolonged APTT	1	0.4%			1	0.4%		
INR increased					1	0.4%		
ALT increased	11	4.2%			3	1.3%		
Bilirubin increased	1	0.4%			3	1.3%		
Hyperglycemia	1	0.4%	1	0.4%	1	0.4%	1	0.4%
Hypokalemia	1	0.4%			1	0.4%		
Hypomagnesemia					1	0.4%		
Hypocalcemia	2	0.8%						
Hypophosphatemia	1	0.4%	1	0.4%	4	1.8%	1	0.4%
Hypokalemia	2	5.0%	1	0.4%	3	1.3%		
Hypomagnesemia	1	0.4%			1	0.4%		
Hypocalcemia	1	1.9%						
Hyperphosphatemia	18	7.1%			9	4.0%		
					19	8.5%		

CONCLUSION

The addition of multiple cycles of i/T to conventional 5 drug therapy for ES is feasible and may be associated with an improved probability for both EFS and OS.

REFERENCES

1. Womer, R.B., et al., *Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group.* J Clin Oncol, 2012. **30**(33): p. 4148-54.
2. Kolb, E.A., et al., *Long-term event-free survival after intensive chemotherapy for Ewing's family of tumors in children and young adults.* J Clin Oncol, 2003. **21**(18): p. 3423-30.
3. Granowetter, L., et al., *Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study.* J Clin Oncol, 2009. **27**(15): p. 2536-41.
4. Houghton, P.J., et al., *Efficacy of topoisomerase I inhibitors, topotecan and irinotecan, administered at low dose levels in protracted schedules to mice bearing xenografts of human tumors.* Cancer Chemother Pharmacol, 1995. **36**(5): p. 393-403.
5. Wagner, L.M., et al., *Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma.* Pediatr Blood Cancer, 2007. **48**(2): p. 132-9.
6. Casey, D.A., et al., *Irinotecan and temozolomide for Ewing sarcoma: the Memorial Sloan-Kettering experience.* Pediatr Blood Cancer, 2009. **53**(6): p. 1029-34.
7. Raciborska, A., et al., *Vincristine, irinotecan, and temozolomide in patients with relapsed and refractory Ewing sarcoma.* Pediatr Blood Cancer, 2013. **60**(10): p. 1621-5.

Ewing Sarcoma Treatment Regimen

Cycle	Localized Stratum	Metastatic Stratum
1	VDC	VDC
2	VDC	VDC
3	VDC	VDC
Local Control	Local Control	Local Control
4	IE	i/T
5	IE	i/T
6	IE	IE
7	VDC	i/T
8	i/T	i/T
9	i/T	IE
10	i/T	i/T
11	i/T	i/T
12	i/T	IE
13	i/T	i/T
14		i/T
15		VDC
16		i/T
17		i/T

VDC: Cyclophosphamide 2.1 g/m2/day x 2 days; Doxorubicin 37.5 mg/m2/day x 2 days; Vincristine 2 mg/m2/day x 1 day; IE: Ifosfamide 2.8 g/m2/day x 5 days; Etoposide 100 mg/m2/day x 5 days; i/T: irinotecan 20 mg/m2/day x 5 days x 2 weeks (10 total doses); Temozolomide 100 mg/m2/day x 5 days;

Poster 158 3007555

THE ADDITION OF CYCLES OF IRINOTECAN/TEMOZOLOMIDE TO CYCLES OF VINCRISTINE, DOXORUBICIN, CYCLOPHOSPHAMIDE (VDC) AND CYCLES OF IFOSFAMIDE, ETOPOSIDE (IE) FOR THE TREATMENT OF EWING SARCOMA (ES).

Paul Meyers[1]*; Emily Slotkin*[1]*; Leonard Wexler*[1]*; Filemon Dela Cruz*[1]
[1]*Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

Objective: Treatment for ES in North America has evolved to include cycles of VDC and IE. A regimen including these 5 agents with interval dose compression has achieved 5 year EFS of 73% for localized ES. At Memorial Sloan Kettering (MSK) we have instead used the strategy of increasing doses of alkylating agents to achieve dose intensification and reported similar results. The combination of irinotecan and temozolomide (i/T) given as irinotecan 20 mg/m2/day for 10 days with temozolomide 100 mg/m2/day for 5 days has achieved objective responses for patients who recur after initial therapy with the 5 drug combination. Our prospective protocol incorporates cycles of i/T with cycles of VDC and IE for the treatment of newly diagnosed patients with ES.

Methods: We designed a prospective trial for the treatment of newly diagnosed patients with Ewing sarcoma. Patients were stratified by the absence (localized) or presence (metastatic) of clinically detectable metastatic disease at initial presentation. For patients with localized ES we administer high dose alkylator therapy with 4 cycles of VDC and 3 cycles of IE, followed by 6 cycles of i/T (Table). For patients who present with metastases we intercalate 10 cycles of i/T with the same 7 cycles of high dose alkylating agent therapy (Table). Local control for the primary tumor is scheduled following cycle 3. Patients with pulmonary metastatic disease receive whole lung radiation following completion of planned systemic therapy. Radiation is administered to all other metastatic sites when possible.

Results: We have enrolled 22 patients with localized and 17 patients with metastatic ES. With a median followup of 16 (5-52) months, patients with localized ES have achieved a 3 year EFS of 95% and overall survival (OS) of 95% (Figure). With a median followup of 21 (2-52) months, patients with metastatic ES have achieved a 3 year EFS of 50% and OS of 70%. Patients with metastatic disease limited to the lungs have a 3 year EFS and OS of 85%.

Conclusion: The addition of multiple cycles of i/T to conventional 5 drug therapy for ES is feasible and may be associated with an improved probability for both EFS and OS.

METHODS

We designed a prospective trial for the treatment of newly diagnosed patients with Ewing sarcoma. Patients were stratified by the absence (localized) or presence (metastatic) of clinically detectable metastatic disease at initial presentation. For patients with localized ES we administer high dose alkylator therapy with 4 cycles of VDC and 3 cycles of IE, followed by 6 cycles of i/T. For patients who present with metastases we intercalate 10 cycles of i/T with the same 7 cycles of high dose alkylating agent therapy.

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6	IE	IE
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8	i/T	i/T
9	i/T	IE
10	i/T	i/T
11	i/T	i/T
12	i/T	IE
13	i/T	i/T
14		i/T
15		VDC
16		i/T
17		i/T

VDC:	**Cyclophosphamide 2.1 g/m²/day x 2 days**
	Doxorubicin 37.5 mg/m²/day x 2 days
	Vincristine 2 mg/m²/day x 1 day
IE:	**Ifosfamide 2.8 g/m²/day x 5 days**
	Etoposide 100 mg/m²/day x 5 days
i/T:	**irinotecan 20 mg/m²/day x 5 days x 2 weeks (10 total doses)**
	Temozolomide 100 mg/m²/day x 5 days

RESULTS

We have enrolled 38 (22 patients=localized and 16 patients=metastatic) patients with ES. Patients enrolled on the localized stratum ranged in age from 5 to 22 (median 15); there were 18 patients with a bone primary and 4 patients with soft tissue primary (Table 4). Patients on the metastatic stratum ranged in age from 7 to 34 (median 17) (Table 5). With a median follow-up of 16 (5-52) months, patients with localized ES have achieved a 3 year EFS of 95% and overall survival (OS) of 95% (figures 1 and 2) With a median follow-up of 21 (2-52) months, patients with metastatic ES have achieved a 3 year EFS o 50% and OS of 70% (figures 3 and 4). Patients with metastatic disease limited to the lungs have a 3 yea EFS and OS of 85%. (figure 5)

-Conferma efficacia della combinazione temozolamide e irinotecan

-utilizzo in prima linea irinotecan orale 5 +5 gg + tmz primi 5 gg

-risultati notevoli: OS metastatici a 3 aa 70%

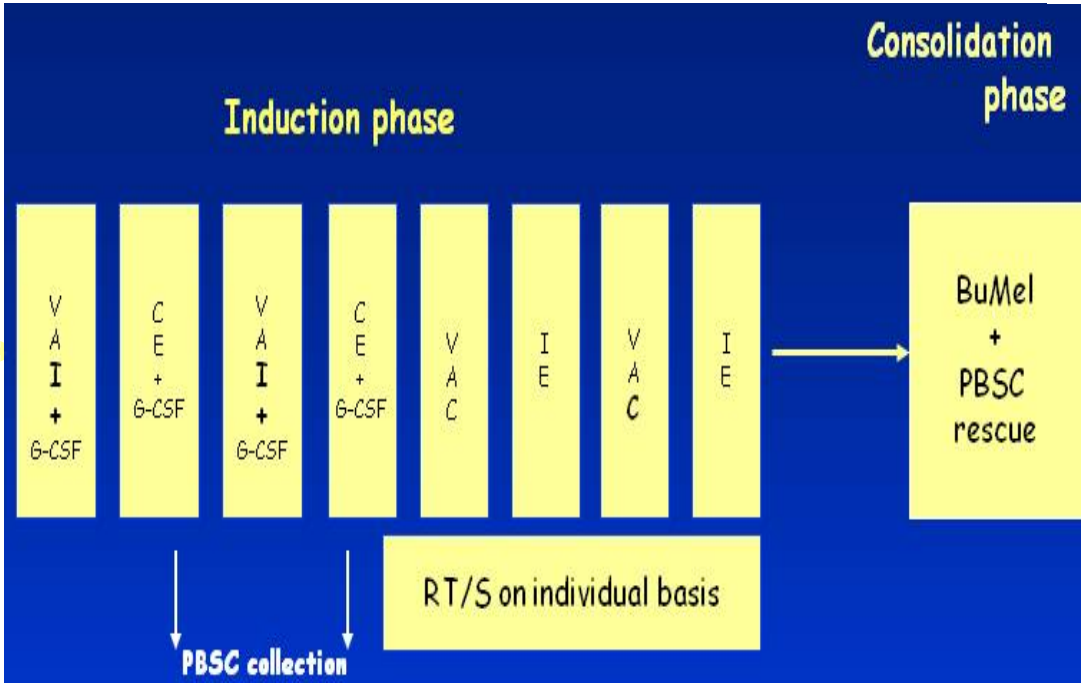
Localizzato: 4 cicli VDC e 3 di IE seguiti da 6 cicli IT

Metastatico: 10 cicli di IT intercalati ai 4 VDC e 3 IE

Very high risk Ewing sarcoma
ISG/AIEOP EW2 v.1.02 Study

front-line

TEMIRI TEMIRI



Maintenance phase

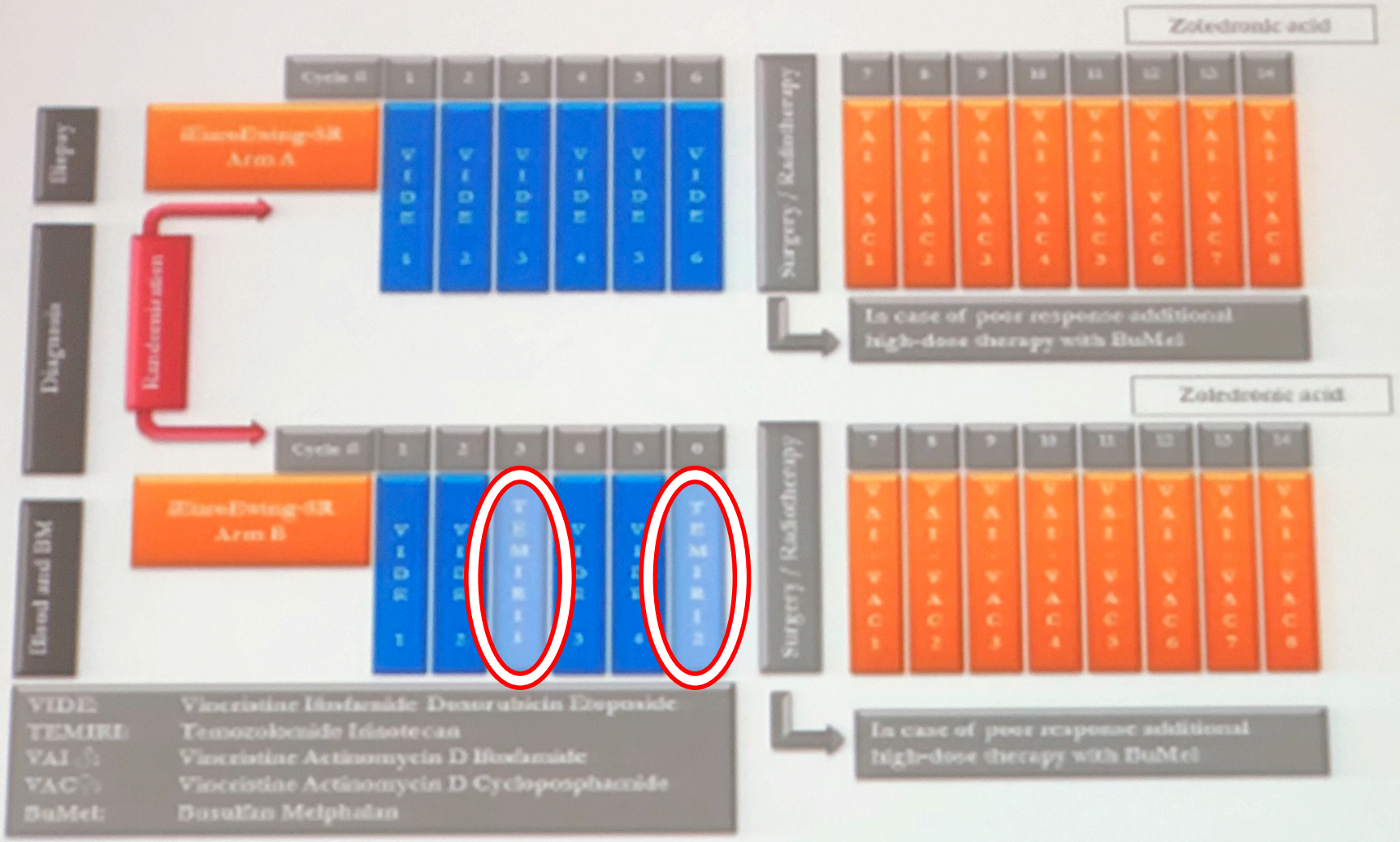
Celecoxib 400mgx2/d
250mg/sqmx2/d in pt <14yrs
+
oral CTX 50mg/d
35mg/sqm in pts pz<14yrs

for 6 months

TEMIRI:

TMZ 100mg/sqm/dx5+IRINO 50mg/sqm/dx5

iEuroEWING (Uta Dirksen)

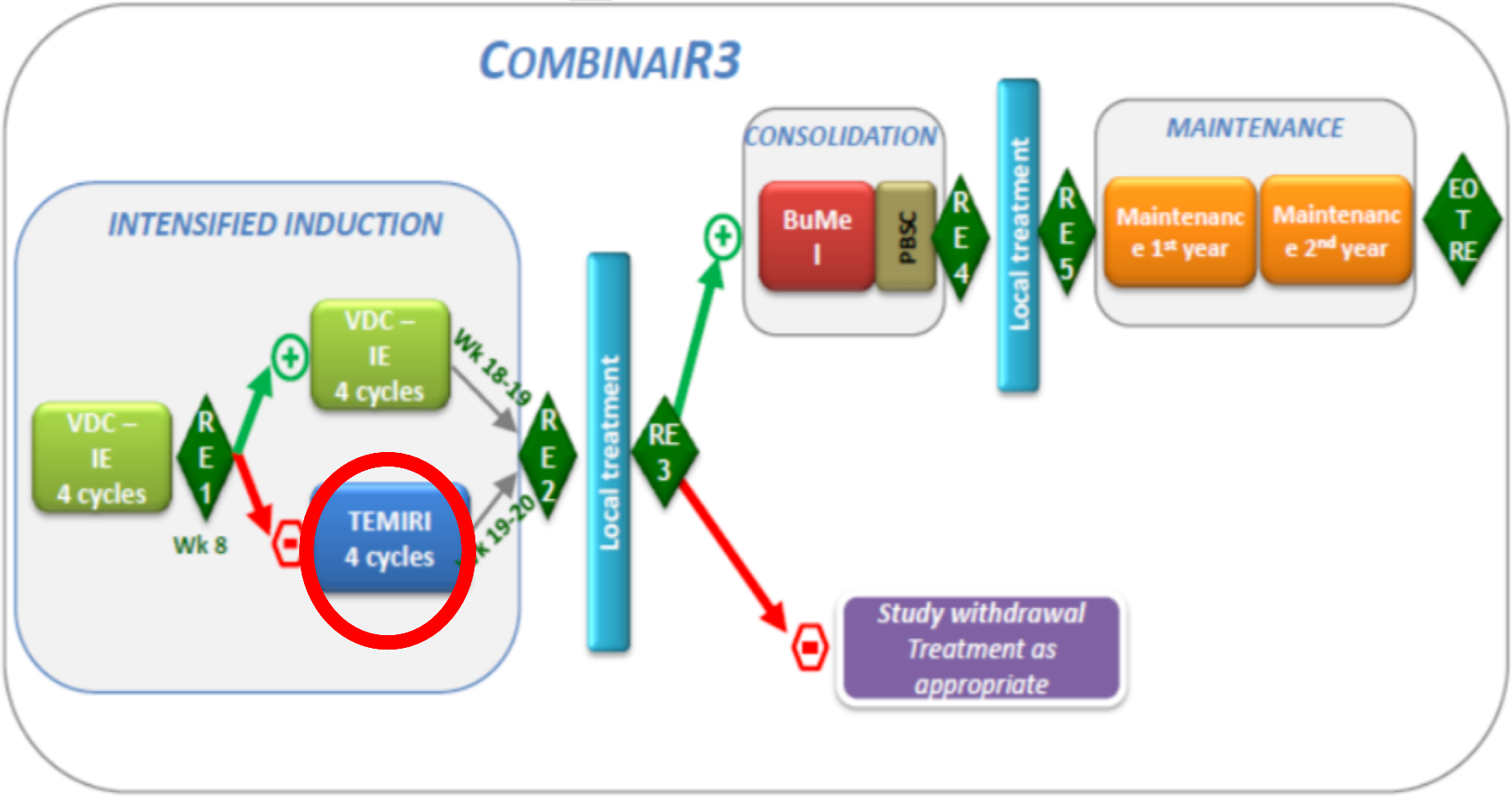


COMBINAIR3

French R3 study

Dr Nadège CORRADINI, pediatrician, IHOP, LYON
Dr Valérie LAURENCE, medical oncologist, head of TYA unit, Institut Curie, PARIS
Didier SURDEZ, PhD, U830, laboratoire O. DELATTRE, Institut Curie, PARIS

COMBINAIR 3



#11519

Efficacy and safety of lurbinectedin (PM1183) in Ewing sarcoma: Final results from a phase 2 study.

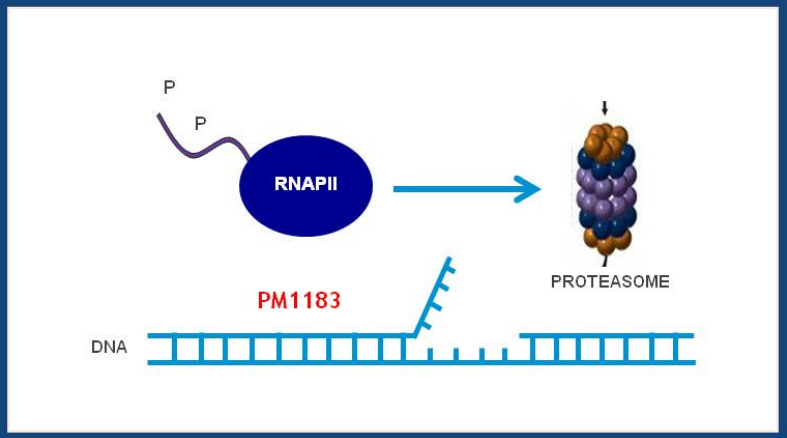
Vivek Subbiah, Kamalesh Kumar Sankhala, Ravin Ratan, Enrique Sanz Garcia, Valentina Boni, Thierry Gil, Victor Manuel Villalobos, Sant P Chawla, Pilar Lardelli, Mariano Siguero, Carmen Maria Kahatt, Arturo Soto-Matos, Stefano Ferrari

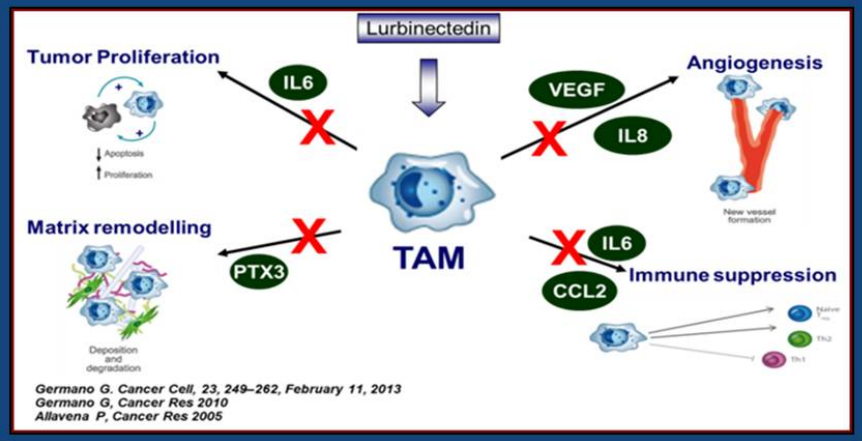
#11519
Efficacy and safety of lurbinectedin (PM1183) in Ewing Sarcoma: Final results from a phase 2 Study
Vivek Subbiah *et al*

- Lurbinectedin 3.2 mg/m2 IV over 1 hour every 3 weeks
- EWS no more than 2 prior chemotherapy regimens
- Phase II

Background: Lurbinectedin

- **Lurbinectedin** is a novel anticancer drug that inhibits active transcription of protein-coding genes and modulates tumor microenvironment.





Molecular Mechanism:
RNA Pol II degradation, accumulation of double strand-breaks
Induction of apoptosis

Tumor Microenvironment Effect
Inhibition of transcription of selected cytokines (e.g. CCL2, IL6, IL8, PTX3) by tumor associated macrophages abrogating their protumoral properties

Results: Baseline Characteristics

		N=28
Age (years)	Median (range)	33 (18-74)
Gender	Male/female	57%/43%
ECOG	UK	1 (3.6%)
	0	11 (39.3%)
	1	15 (53.6%)
	2	1 (3.6%)
Tumor type	Bone	11 (39.3%)
	Extraosseous	15 (53.5%)
	UK	2 (7.1%)
Sites of disease involvement	<3	21 (75%)
	≥3	7 (25%)
Prior chemotherapy lines (any setting)	1	4 (14.3%)
	2	16 (57.1%)
	>2	7 (28.6%)

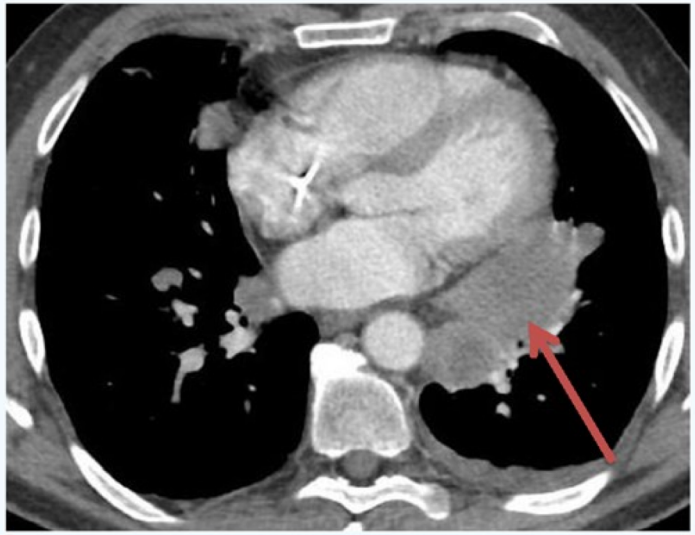
Response and Disease Control

Response Evaluable patients	N=28
CR	-
PR	**5 (18%)**
ORR	5 (18%)
SD≥ 4 months	6 (21%)
SD< 4 months	5 (18%)
PD	12 (43%)
DCR	16 (57%)
Median DOR* (weeks)	11.6
Median PFS (months)	2.8

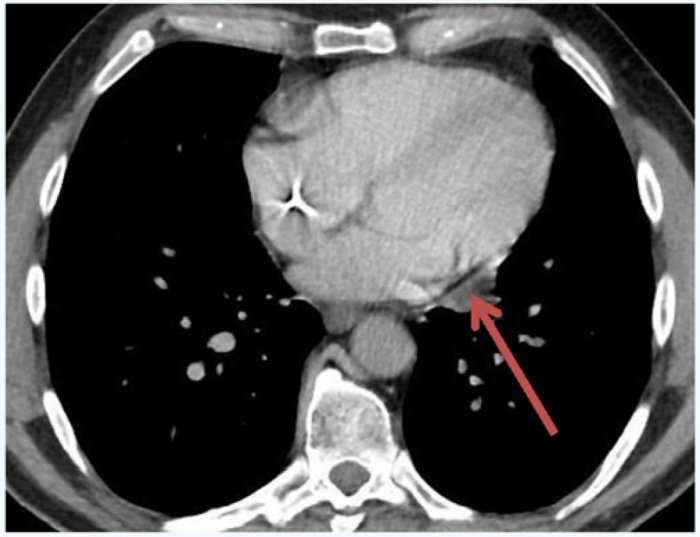
D, day; DCR, disease control rate; DOR*, duration of response (descriptive); PFS, progression free survival (K-M).

Response and Disease Control

CT Pre- and Post Images of a 54 Year Old Patient with Ewing's Sarcoma Metastatic to the Lungs Showing Response to Therapy



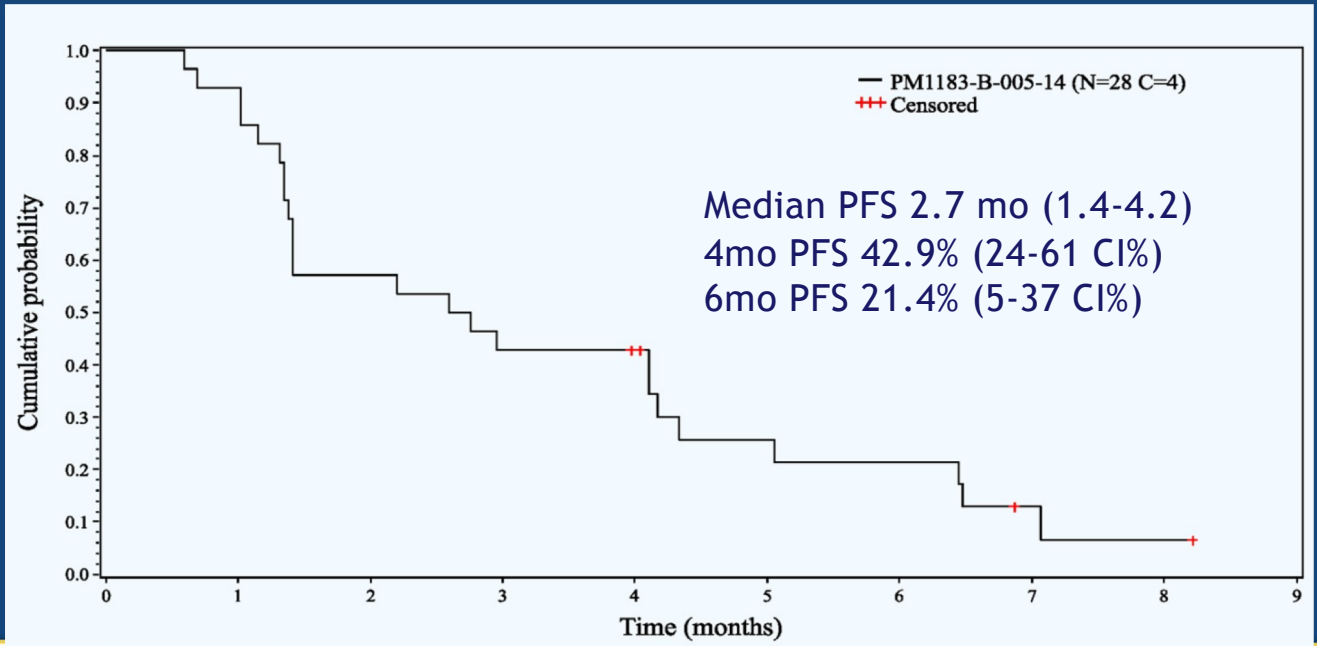
Baseline (13/01/2017)



Post Cycle 2 Lurbinectedin (03/03/2017)

Courtesy of Dr. C. Gómez-Roca and Prof. JP Delord. Institute Universitaire du Cancer de Toulouse, Oncopole (France)

Progression free survival in Ewing Sarcoma pts (n=28)



Safety

Adverse events CTC grade v4.0*	1	2	3	4	Total
	n (%)	n (%)	n (%)	n (%)	N (%)
Fatigue	7 (25)	3 (11)			10 (36)
Nausea	7 (25)	1 (3.6)			8 (26)
Vomiting		1 (3.6)			1 (4)
Diarrhoea	3 (11)				3 (11)
Constipation	1 (3.6)				1 (3.6)
Febrile Neutropenia			2 (7)	2 (7)	4 (14)
Anemia	13 (46)	6 (21)	5 (18)		24 (86)
Neutropenia		4 (14)	5 (18)	10 (36)	19 (68)
Thrombocytopenia	9 (32)	2 (7)	4 (14)		15 (54)
ALT	14 (50)	4 (14)	2 (7)		20 (71)
AST	13 (46)	1 (3.6)			12 (48)

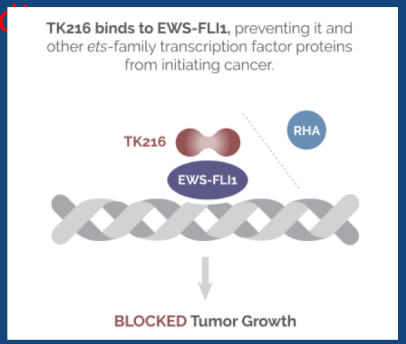
*Treatment-related adverse events (≥ 10% of patients or grade ≥3). ** Laboratory abnormalities regardless relationship.
Use of G-CSF: 12 patients (43%).
Patients with drug related administration delays: 7 (25%)
Patients with drug related dose reductions: 6 (21%)

Ewings Sarcoma: What is the Correct Target?

- Targeted therapy
- Precision medicine
- EWS transcription factor fusion gene
  - EWSR1 on chromosome 22q12
  - FLI1 on Chromosome 11
- Ewing Family of Tumors
  - DSRCT
  - CIC-DUX
  - BCOR-CCNB3

IGF-1R + BRD4i[1], niraparib + IRI[2], PARPi+ NPTransferase[3], LSD1[4,5]

PEWbi-shRNA™ EWS/FLI1 Type 1
LPX
TK216
Lurbinectedi



LSD1=lysine-specific demethylase

[1]Mancarella C et al, Cli Can Res 2018
[2]Chugh R et al, CTOS 2017
[3]Iniguez AB et al, Cancer Cell 2018
[4]Bennani-Baiti IM. Hum Pathol. 2012
[5]clinicaltrials.gov/ct2/show/NCT03514407

Cortesia E Palmerini

Paper 035 3042245

A PHASE I STUDY OF THE POLY-ADP RIBOSE POLYMERASE (PARP) INHIBITOR, NIRAPARIB (NIR), IN COMBINAITON WITH IRINOTECAN (IRN) IN PATIENTS WITH ADVANCED EWING SARCOMA: RESULTS OF SARC025 ARM 2

Sandra J. Strauss[1]; Karla V Ballman[2]; Kam Zaki[1]; Lee Helman[3]; Brigitte Widemann[4]; Douglas Hawkins[5]; Leo Mascarenhas[3]; J.W Glod[4]; Jay Ji[6]; Ziping Zhang[6]; Birgit Geoerger[7]; Jeremy Whelan[1]; Denise Reinke[8]; Shreyaskumar Patel[9]; Rashmi Chugh[10]

[1]University College London Hospitals NHS Trust, London, United Kingdom; [2]Weill Cornell Medicine, New York, NY, USA; [3]Children's Center for Cancer and Blood Diseases, Los Angeles, CA, USA; [4]National Cancer Institute Centre for Cancer Research, Bethesda, MD, USA; [5]Seattle Children's Hospital, Seattle, OR, USA; [6]National Clinical Target Validation Laboratory, Bethesda, MD, USA; [7]Institut Gustave Roussy, Paris, France; [8]SARC, Ann Arbor, MI, USA; [9]MD Anderson, Houston, TX, USA; [10]University of Michigan, Ann Arbor, MI, USA

- » Fase 1
- » Dose corretta NIR 100 mg qd 1-7 gg e IRN 20 mg/mq 2-6 gg cicli ogni 28 gg
- » Su 10 pz 1 RP e 4 SD; mPFS 4.9 mesi
- » Aggiunta TMZ?

Results: Between Nov 2016 and May 2018, 12 eligible patients (9 male) with confirmed EWSR1-FLI1 translocation positive Ewing sarcoma were enrolled at 2 dose levels. Median age was 27 years (range 16-50); median prior therapies 4 (range 1-9) with 7 patients having received prior IRN. At time of data cutoff, the median number of cycles was 2 (range 1 - 17). DLTs were observed in all 3 patients at dose level 1 (1 pt each with grade 3 anorexia, grade 3 colitis, and grade 3 transaminitis). No DLTs were reported in 7 evaluable patients treated at NIR 100mg and IRN 20mg/m^2 (dose level -1); 2 patients experienced transient grade 3 neutropenia and 1 patient grade 3 gastro-intestinal toxicity (diarrhea, abdominal pain, nausea and vomiting lasting < 72 hours) and grade 3 thrombocytopenia. In 10 evaluable patients, best response was partial response in 1 patient, stable disease in 4 patients, and progressive disease in 5 patients. Median progression-free survival was 4.9 months (range 1.18-NR). Pharmacodynamic analysis of tumor samples demonstrated > 80% PARP inhibition across all doses of NIR.

Conclusion: NIR 100 mg qd D1-7 in combination with IRN 20mg/m^2 was well tolerated with preliminary evidence of efficacy that warrants further investigation. Patient biopsy was feasible and pharmacodynamic analysis supported the recommended phase 2 dose. Further cohorts incorporating temozolomide are planned and additional correlative analysis is ongoing.

Paper 036 3035962

SLFN11 IS A SIGNIFICANT DETERMINANT OF PARP INHIBITOR SENSITIVITY IN PEDIATRIC SARCOMAS

Jessica Gartrell; Marcia M. Mellado-Largarde; Jia Xie; Brandon Bianski; Kaley Blankenship; Michael Clay; Armita Bahrami; Sara Federico; Christopher L. Tinkle; Elizabeth Stewart; Anang Shelat
St. Jude Children's Research Hospital, Memphis, TN, USA

» SLFN11 biomarker di sensibilità a PARPi

» Transfezione, xenografts

» Testati TAL talazoparib PARPi + IRN + TMZ

» cell esprimenti SLFN11 sensibili a TAL 90%

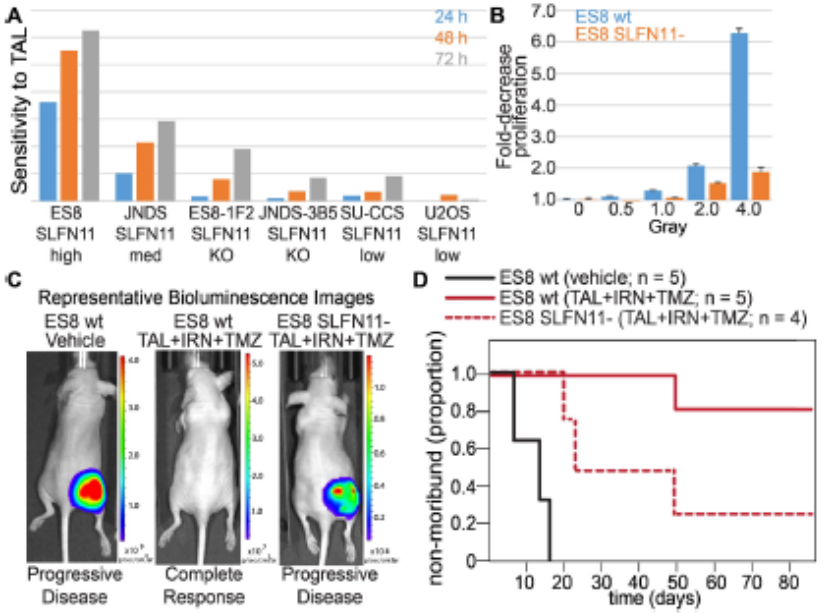


Figure 1. (A) CTG assay revealed a positive correlation between SLFN11 levels and sensitivity to the PARPi TAL. **(B)** ES8 SLFN11 KO cells were more resistant to ionizing radiation, and showed less than a two-fold loss of cell proliferation compared to a greater than six-fold decrease for wild-type cells at 4Gy. (C) Representative bioluminescence from in vivo studies demonstrating increased tumor burden in ES8 SLFN11 KO mice xenograft models. (D) Kaplan-Meier curve demonstrating decreased survival in ES8 SLFN11 KO mice xenograft models.

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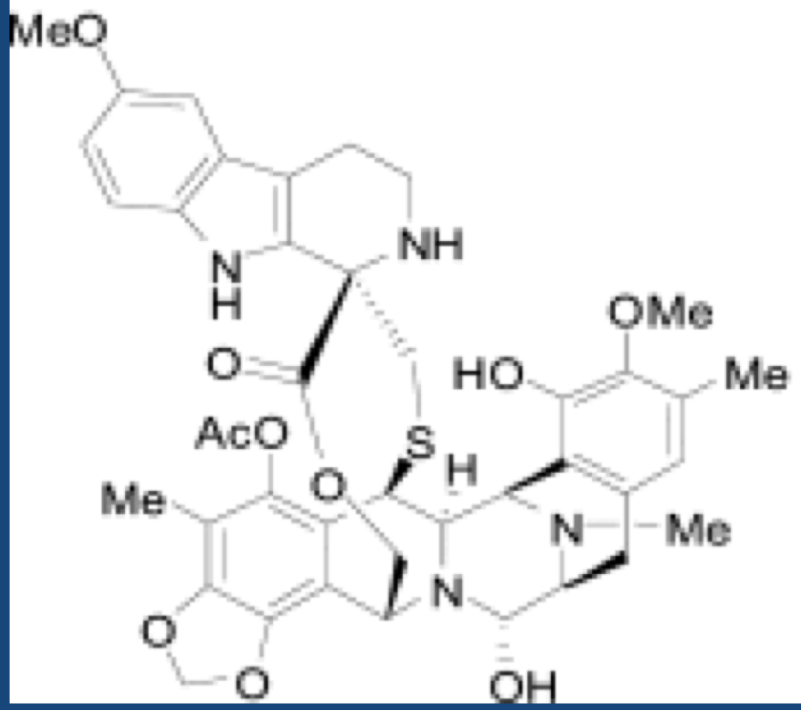
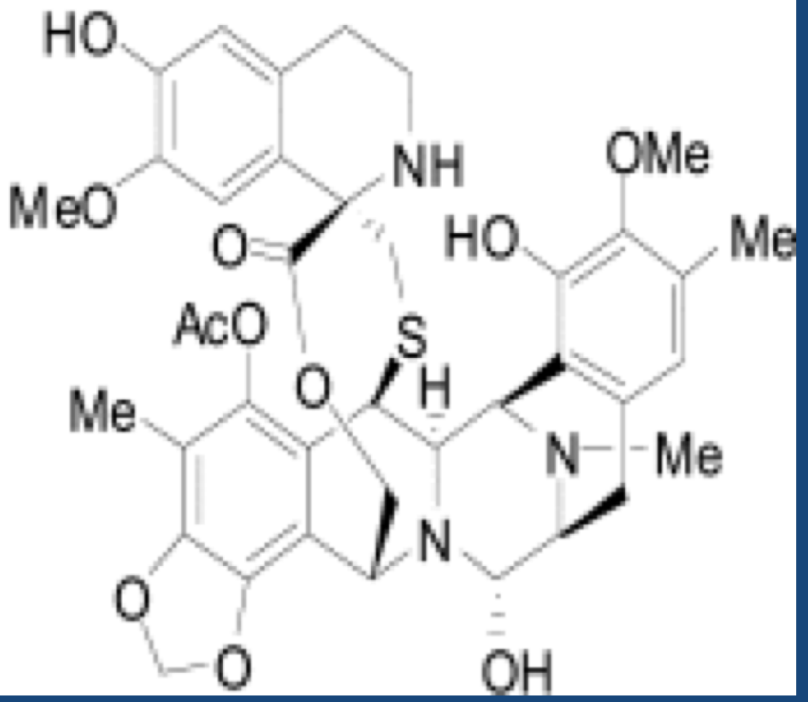
Lurbinectedin

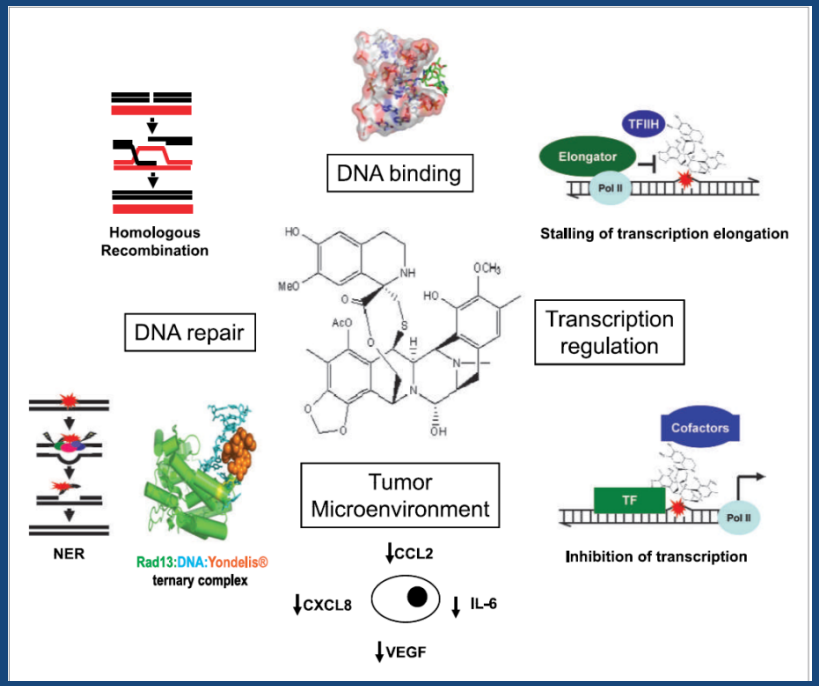


Trabectedin



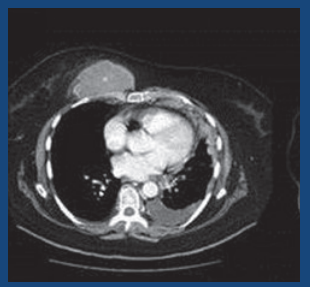
Cortesia E Palmerini

Conclusion: Trabectedin in EW

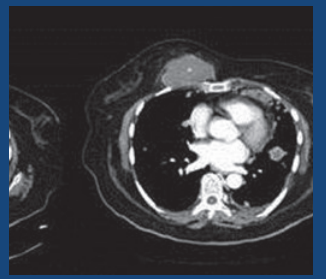


- Trabectedin COG:0 PR/16 EWS
- Tabectedin + Olaparib ph I
  0 PR/4 EWS
- Trabectedin case report

Baseline



21 months



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY:

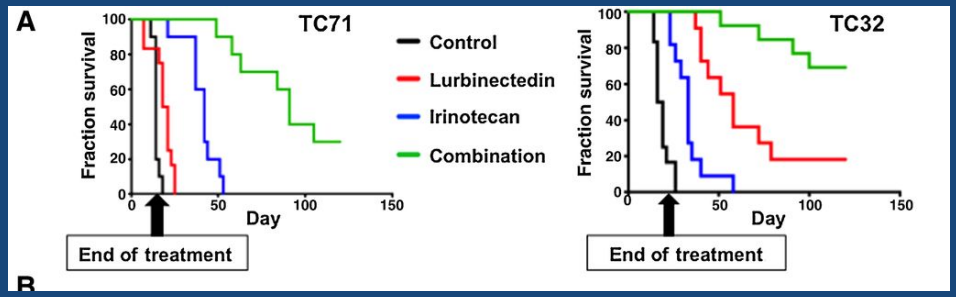
D' Incalci M et al, Mol Cancer 2010

Baruchel S et al, 2E J of Cance 2012
Grignani G et al, ASCO 2016
Hernando-Cubero J et al, Onc Lett 2016

Cortesia E Palmerini

Conclusion: Lurbinectedin in EW

- Inactivates the Ewing Sarcoma Oncoprotein EWS-FLI1
- Promising for selected patients with EWS
- Monotherapy: 5/28 (18%) PR
- Combo + irinotecan?



Harlow ML, Can Res 2018

Cortesia E Palmerini

A Phase 1/2 single-arm study evaluating the safety and efficacy of eribulin mesilate in combination with irinotecan in children with refractory or recurrent solid tumors

Study 213: Rationale

Anti-microtubule agents have shown moderate single-agent activity against RMS in the clinic and the laboratory – this is significantly enhanced in combination with alkylating agents or camptothecins.

Substituting the anti-microtubule agent, eribulin, which has been found to be more potent in preclinical models than vincristine, as a combination partner with irinotecan will result in substantial efficacy against RMS, NRSTS and EWS.

It should be possible to use a regimen of eribulin and irinotecan (ie, replace vincristine) considering that the primary toxicity profiles of each individual agent do not overlap, the synergy observed when irinotecan is combined with a microtubule inhibitor, and the activity observed for eribulin in the solid tumor panels (seen in preclinical testing) is comparable or superior to that observed previously for vincristine.

Cortesia C Favre

Pediatric versus adult patients with Ewing sarcoma

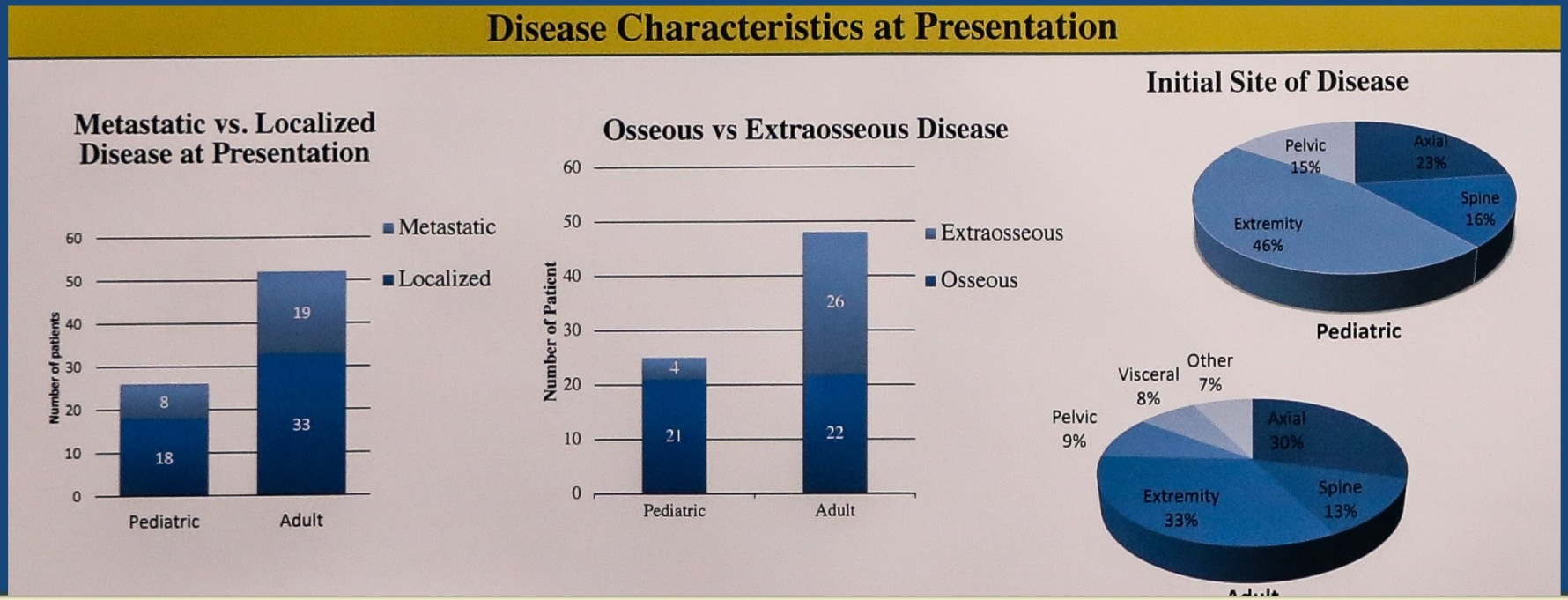
Eric B Schwartz, Lili Zhao, Brittany Siontis, Laurence H. Baker, Rama Rao, Elizabeth R. Lawlor, Scott Schuetze, Rashmi Chugh

» University of Michigan

» From 2007-15

» 78 patients: 26 ped, 56 adu
27 met, 55 loc

Pediatric versus adult patients with Ewing sarcoma



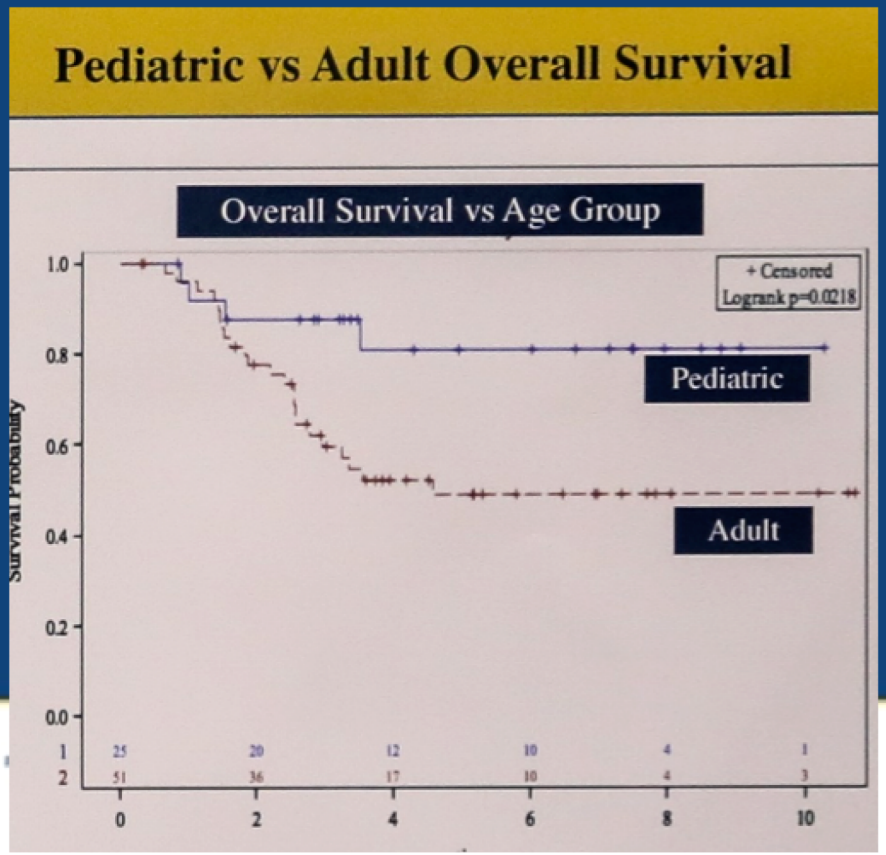
Pediatric versus adult patients with Ewing sarcoma

Kids:

- More chemo
- Less doxorubicin
- Bone > STS

Variable	Age <=18	Age > 18	p-value
Localized Disease at Presentation, n (%)	17 (65.4)	33 (63.5)	0.8674
Average number of Adjuvant/Neoadjuvant cycles	14.0	11.8	**0.0027**
Mean Cumulative Doxorubicin (mg/m2)	357.9	445.6	**<0.0001**
Osseous primary site n (%)	21 (84)	22 (45.8)	**0.0017**
Tumor size cm mean (range)	8.17 (3.2 – 19.3)	9.51 (1.8 – 23.5)	0.3843

Pediatric versus adult patients with Ewing sarcoma



Loc
+
Met

Younger age better
5 year OS
81% adult

49% pediatric

http://clicktoeditURL.com

OsteoSarcoma

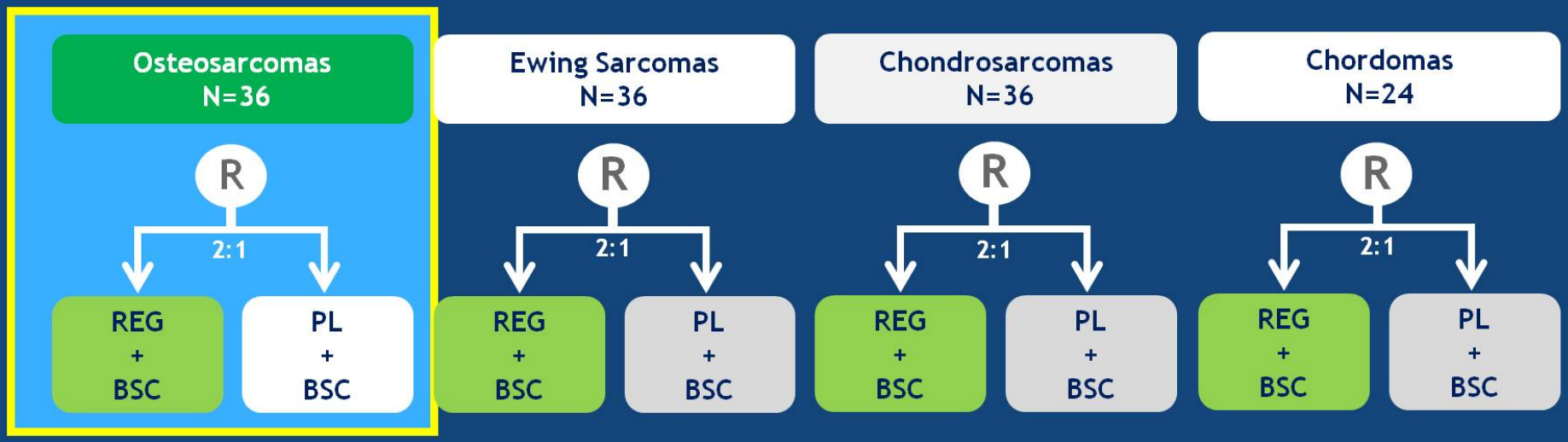
#11504

Results of randomized, Placebo (PL) - controlled Phase II study evaluating efficacy and safety of Regorafenib (REG) in patients (pts) with metastatic Osteosarcoma (metOS), on behalf of the French Sarcoma Group (FSG) and Unicancer

Duffaud F, Blay JY, Mir O, Boudou-Rouquette P, Piperno-Neuman S, Penel N, Bompas E, Delcambre C, Kalbacher E, Italiano A, Collard O, Chevreau C, Thyss A, Isambert N, Delaye J, De Sousa Carvalho N, Schiffler C, Bouvier C, Vidal V, Chabaud S.

REGOBONE: study design
Regorafenib for Advanced/Metastatic Bone Sarcomas

- **Basket of 4 parallel *non-comparative* randomized phase II trials**



REGORAFENIB or PLACEBO dosed until progression or unacceptable toxicity

Pts initially randomized to PL could cross-over to open-label REG after PD confirmation

Osteosarcoma in REGOBONE: Study Design / Statistics

- Endpoints:
  - **Primary endpoint: Non-progression rate at 8 weeks**
  - Secondary end points:
  - PFS (per modified RECIST 1.1), OS, Toxicity (according to NCI-CTC AE V4)

- Statistical Design per A'Hern's single-stage design for phase II trials (A'Hern et al 2001)
  - P0 40%, P1 67% (based on Qi WX et al 2012, Chou AJ et al 2012, Ebb D et al 2012, Laverdiere F et al 2003)
  - One-sided α: 5% ; β = 80%
  - → 24 patients needed in REG arm (≥ 14 NP pts at 8 weeks for 'success')
  - 2:1 Randomization → 36 patients total randomized population
  - No formal statistical comparison between REG and PL

Osteosarcoma in REGOBONE: Key eligibility criteria

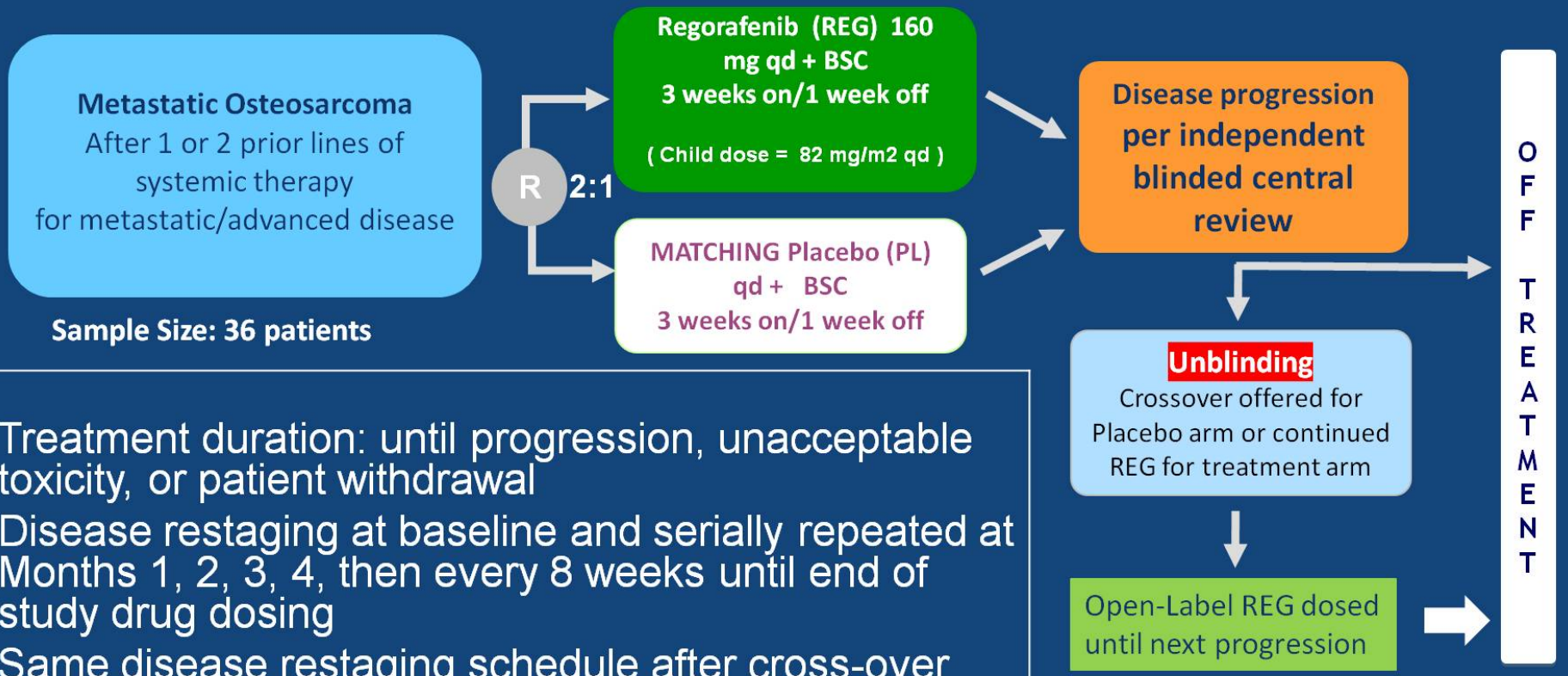
- **Main inclusion criteria**
- Histologic **centrally-confirmed diagnosis*** of high grade OS
- **Progressive disease in 3 months** prior to study entry
- Metastatic /local. advanced disease not amenable to surgery or radiation with curative intent
- Measurable disease (RECIST 1.1)
- Prior treatment required: at least 1, but no more than 2 prior (combination) chemo regimen for metastatic disease
- Age ≥ 10 years **
- ECOG PS < 2 (Karnofsky ≥ 60%)
- Adequate bone marrow, liver, renal, cardiac functions
- Dated + signed informed consent form

- **Main exclusion criteria**
- **Prior treatment with any VEGFR inhibitor**
- Significant cardiovascular dysfunction:
  - Congestive heart failure
  - Myocardial infarction <6 months before study
  - Cardiac arrhythmias requiring therapy
  - Uncontrolled hypertension
  - Unstable or new-onset angina
- Other cancer (different histology) within 5 years prior to randomization
- Major surgical procedure, open biopsy, or significant trauma <28 days before study

* Available Formalin Fixed Paraffin Embedded (FFPE) blocks obtained for centralized review

** Amendment: Children with BSA ≥ 1.30 m2 enrolled

Osteosarcoma in REGOBONE: study plan



- Treatment duration: until progression, unacceptable toxicity, or patient withdrawal
- Disease restaging at baseline and serially repeated at Months 1, 2, 3, 4, then every 8 weeks until end of study drug dosing
- Same disease restaging schedule after cross-over

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PRESENTED BY: Florence Duffaud

Osteosarcoma in REGOBONE: Baseline Patient characteristics (1)

		Regorafenib N= 26	Placebo N=12
Age, median years (range)		32 (18–74)	40 (22–64)
Sex, n (%)	Male	19 (73.1)	5 (41.7)
	Female	7 (26.9)	7 (58.3)
Prior lines of OS therapies for metastatic disease, n (%)	1	21 (80)	10 (83)
	2	5 (20)	2 (17)
ECOG, n (%)	0	12 (46)	2 (16.7)
	1	14 (54)	10 (83.3)
Presence of metastases, n (%)	No (locally advanced disease)	1 (3.8)	0
	Yes	25 (96.2)	12 (100)

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

Demetri et al. ASCO 2012

PRESENTED BY: Florence Duffaud

Osteosarcoma in REGOBONE: Baseline Patient characteristics (2)

	Regorafenib N= 26	Placebo N=12
Lung metastasis	24 (92%)	10 (83%)
Bone metastasis	6 (23)	3 (25)
Lymph nodes metastasis	3 (11.5)	4 (33.3)
Pleural metastasis	3 (11.5)	1 (8.3)
Previous Therapy at entry		
Doxorubicin	26 (100)	12 (100)
Ifosfamide	24 (92)	12 (100)
Cisplatin	25 (96)	11 (91.6)
HD Methotrexate	7 (27)	3 (25)
Etoposide	21 (81)	5 (41.6)
Gemcitabine/Docetaxel	3 (11.5)	2 (1.6)
Oral Cychlophosphamide	3 (11.5)	1 (0.8)

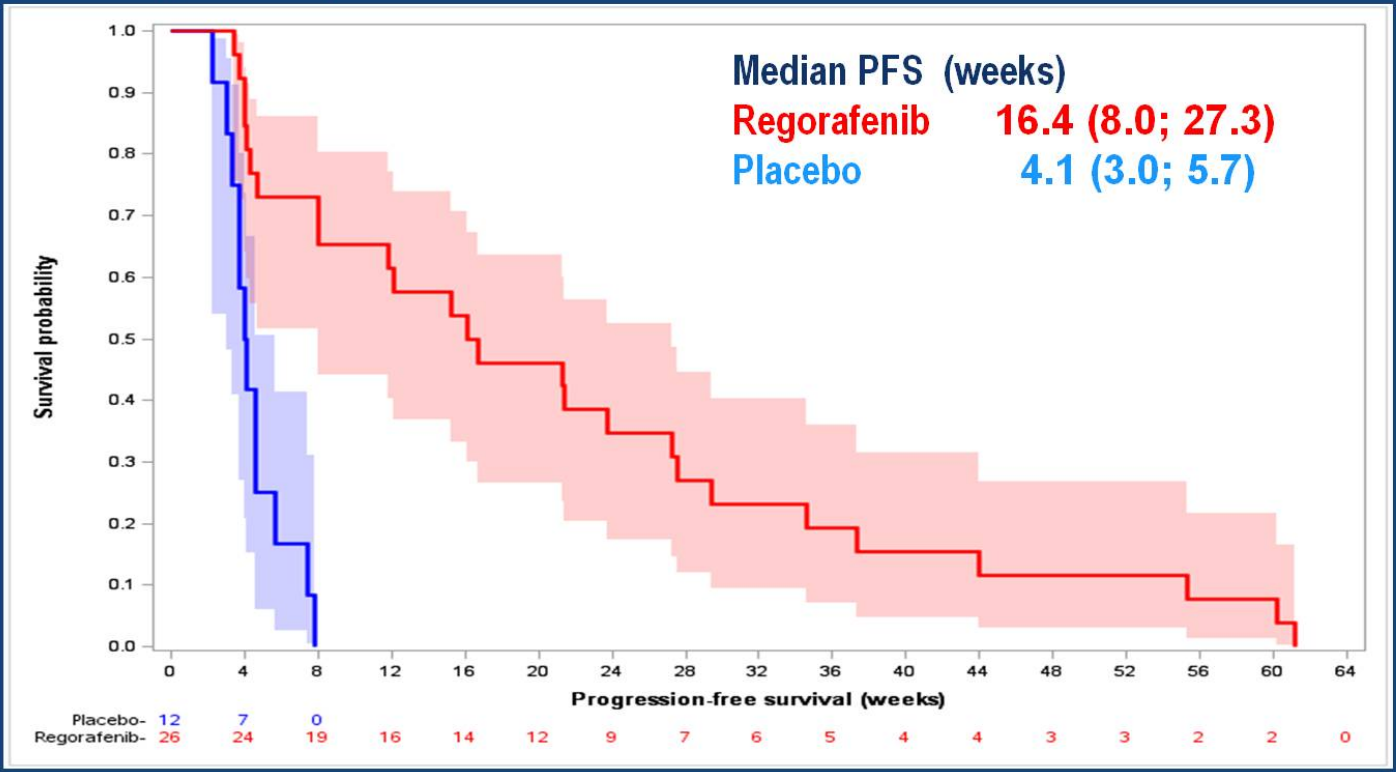
Osteosarcoma in REGOBONE: Results

		Regorafenib N= 26	Placebo N=12
Non progressive rate at 8 weeks (%) One –sided Confidence Interval (CI95%)		**17 (65.4)** (47.4; -)	**0** (0;-)
Response at 8 weeks (%)	PR*	2 (7.7)	0
	SD	15 (57.7)	0
	PD	9 (34.6)	12 (100)
Median PFS (CI 95%) (weeks)		**16 (8.0; 27.3)**	**4 (3.0; 5.7)**
PFS rate at 12 weeks (CI95%)		62 (40; 77)	0
PFS rate at 24 weeks (CI95%)		35 (17; 52)	0

* 2 PR: duration of responses of 12.9 and 6.2 months

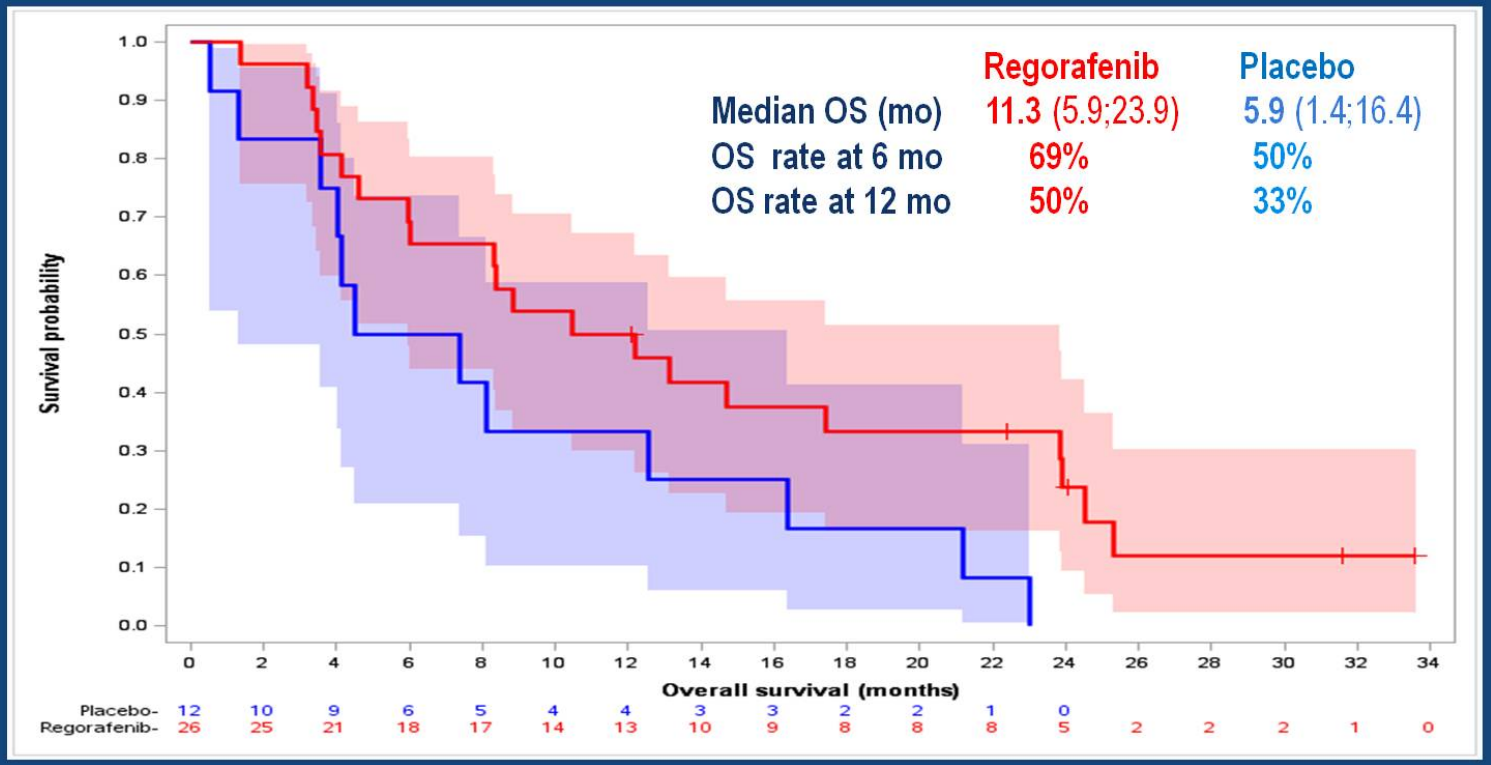
Osteosarcoma in REGOBONE: Progression-Free Survival

Primary end-point per blinded central review

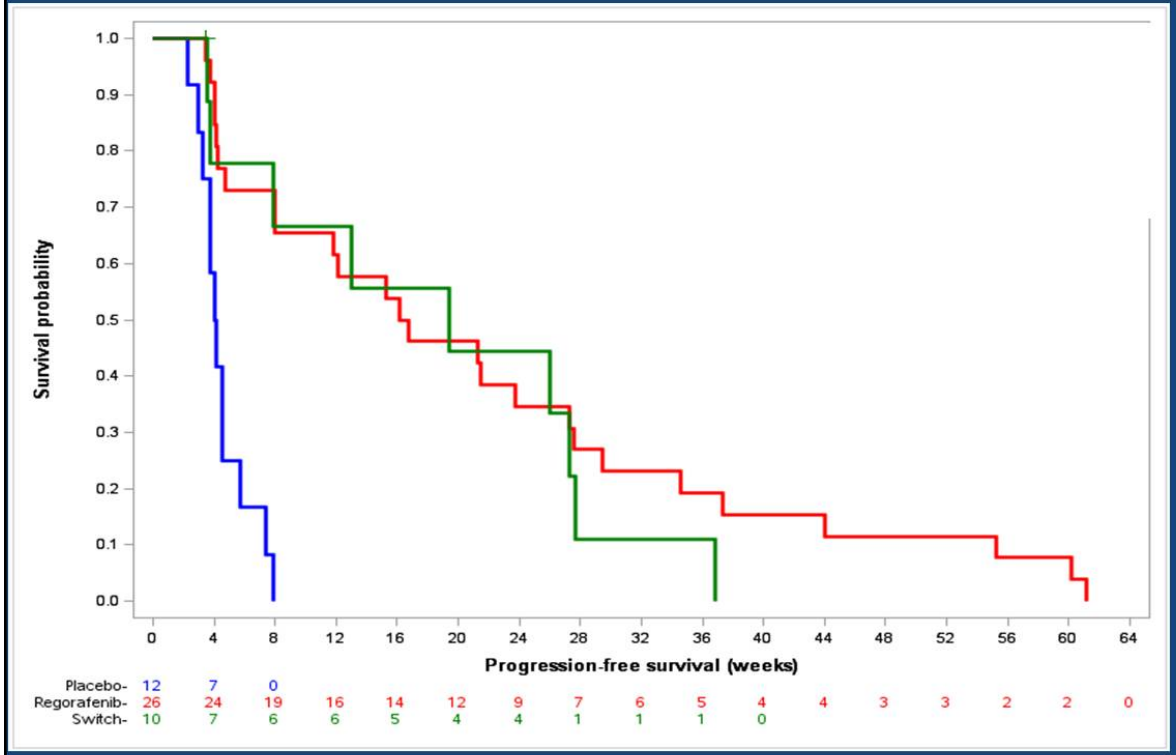


Osteosarcoma in REGOBONE: Overall survival (OS)

following cross-over in 83% of pts initially on placebo



Osteosarcoma in REGOBONE: Progression-Free Survival from randomisation (central review) and following cross over (per investigator assessment)



10/12 patients on PL arm crossed over*

	Placebo	Rego	Rego post switch
Median PFS	4 (3;5.7)	16.4 (8;27.3)	19.4 (3.5;27.7)
PFS rate at 12 wks	0	62 (40-77)	66 (28-88)
PFS rate at 24 wks	0	35 (17-52)	44 (14-72)

* 2 pts on PL did not cross over:
1 study withdrawal,
1 non centrally confirmed PD, died 16 days after incl

Most frequent drug-related treatment-emergent adverse events in patients during double-blind treatment

All pts enrolled		Regorafenib (N=29), % Median exposure : 3.4 months Median dose 120 mg (65-160)		Placebo (N=14), % Median exposure : 1.1 months Median dose 120 mg (96-175)	
	Grade	All	≥ 3	All	≥ 3
Hand-foot skin reaction		15 (51.7)	**3 (10.3)**	1 (7.1)	**0**
Hypertension		12 (41.4)	**7 (24.1)**	2 (14.3)	**0**
Diarrhea		13 (44.8)	**2 (7)**	1 (7)	0
Fatigue		26 (89.7)	**3 (10.3)**	7 (50)	1 (7.1)
Anorexia		10 (34.5)	1 (3.4)	1 (7.1)	1 (7.1)
Constipation		11 (37.9)	2 (6.9)	0	0
Hypophosphatemia		5 (17.2)	**3 (10.3)**	0	0

Osteosarcoma in REGOBONE: Conclusions (1)

- Results indicate a very promising signal of benefit with regorafenib for metastatic osteosarcoma pts after failure of prior chemotherapy
- Primary end-point: non-progressive rate at 8 weeks
  - 65.4% with regorafenib; 0% with placebo
- Median PFS
  - 16.4 weeks with regorafenib; 4.1 weeks with placebo
- Confirmatory pattern of longer time to progression after cross-over to open-label regorafenib in pts initially randomized to placebo

Osteosarcoma in REGOBONE: Conclusions (2)

- A placebo controlled randomized trial is *feasible and acceptable* in patients with metastatic osteosarcoma
  - Rapidly reached full accrual
- Metastatic osteosacoma confirmed as a very agressive disease
  - Median PFS of 4 weeks in PL arm: worst than our null hypothesis (median PFS of 6 weeks)
- Toxicity of regorafenib was as expected and quite acceptable

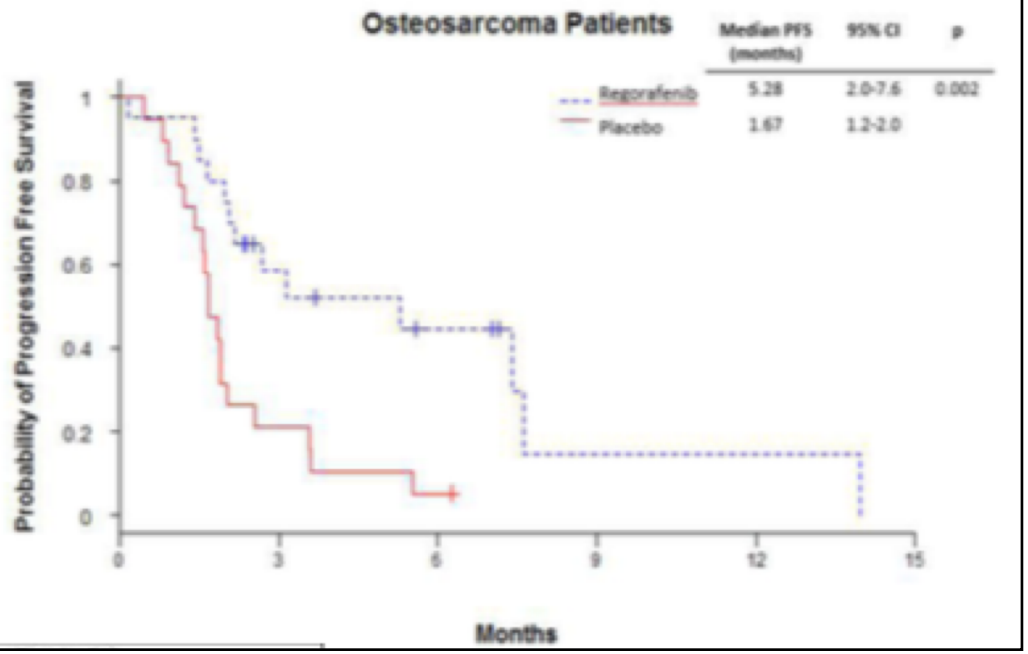
Paper 041 3042511

SARC024: REGORAFENIB IN PATIENTS WITH REFRACTORY OSTEOSARCOMA

Lara E. Davis[1]; *Christopher Ryan*[1]; *John Crowley*[2]; *Kristen Ganjoo*[3]; *Elizabeth Loggers*[4]; *Sant P. Chawla*[5]; *Mark Agulnik*[6]; *Michael B. Livingston*[7]; *Damon Reed*[8]; *Vicki Keedy*[9]; *Daniel A. Rushing*[10]; *Scott Okuno*[11]; *Denise Reinke*[12]; *Richard F. Riedel*[13]; *Steven Attia*[14]; *Leo Mascarenhas*[15]; *Robert Maki*[16]

[1]*Oregon Health and Science University, Portland, OR, USA;* [2]*Cancer Research and Biostatistics, Seattle, WA, USA;* [3]*Stanford Cancer Institute, Stanford, CA, USA;* [4]*Seattle Cancer Care Alliance, Seattle, WA, USA;* [5]*Sarcoma Oncology Research Center, Santa Monica, CA, USA;* [6]*Northwestern University Feinberg School of Medicine, Chicago, IL, USA;* [7]*Levine Cancer Institute, Atrium Health, Charlotte, NC, USA;* [8]*H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA;* [9]*Vanderbilt University Medical Center, Nashville, TN, USA;* [10]*Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, USA;* [11]*Mayo Clinic, Rochester, MN, USA;* [12]*SARC, Ann Arbor, MI, USA;* [13]*Duke University Medical Center, Durham, NC, USA;* [14]*Mayo Clinic, Jacksonville, FL, USA;* [15]*Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Univ. of Southern California, Los Angeles, CA, USA;* [16]*Monter Cancer Center, Northwell Health and Cold Spring Harbor Laboratory, Lake Success, NY, USA*

- » regorafenib 160 mg/die x 21gg ogni 28 vs placebo (cross-over alla PD)
- » mPFS 5.3 mesi vs 1.7
- » mOS 26.7 mesi
- » 69% tossicità grado 3-4



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Single-agent Expansion Cohort of Lenvatinib (LEN) and Combination Dose-finding Cohort of LEN + Etoposide (ETP) + Ifosfamide (IFM) in Patients (pts) Aged 2 to ≤ 25 Years With Relapsed/Refractory Osteosarcoma (OS)

Nathalie Gaspar,[1] Michela Casanova,[2] Francisco José Bautista Sirvent,[3] Rajkumar Venkatramani,[4] Bruce Morland,[5] Marion Gambart,[6] Estelle Thebaud,[7] Sandra J. Strauss,[8] Franco Locatelli,[9] Soledad Gallego Melcon,[10] Adela Canete Nieto,[11] Stefan Bielack,[12] Claudia Rossig,[13] Isabelle Aerts,[14] Perrine Marec-Berard,[15] Silvija Kraljevic,[16] Seiichi Hayato,[17] Cixin He,[18] Corina Dutcus,[18] Quentin Campbell-Hewson[19]

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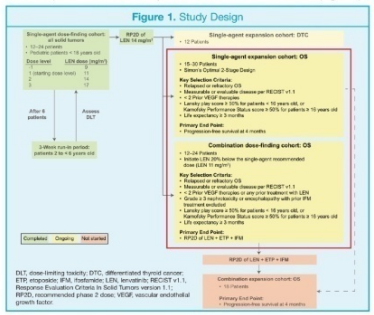
INTRODUCTION

- First-line treatment of osteosarcoma (OS), the most common primary malignant bone tumor in children and young adults, consists of surgical resection with adjuvant and neoadjuvant chemotherapy.[1]
- The rate of OS relapse is approximately 30% for patients with localized disease and 80% for patients presenting with metastatic disease.[1]
  - The optimal treatment strategy for patients with relapsed or refractory disease remains undefined.
  - Several chemotherapeutic agents are recommended as second-line therapy, including etoposide (ETP) and ifosfamide (IFM).
- Antiangiogenic tyrosine kinase receptor inhibitors may offer the possibility of enhancement of conventional chemotherapy or single-agent therapy with a more manageable safety profile.[2]
  - Lenvatinib (LEN) is an oral tyrosine kinase receptor inhibitor targeting vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor alpha, RET, and KIT.[3]
  - In preclinical studies, LEN + IFM + ETP enhanced the antitumor activity of both single-agent LEN therapy and IFM + ETP combination therapy.[4]
- Previously, we reported results from the single-agent dose-finding cohort of LEN in pediatric patients with solid tumors, in which the recommended phase 2 dose was determined to be LEN 14 mg/m².[5]
- Here, we report emerging data from a phase 2 single-agent LEN expansion cohort and a phase 1b combination dose-finding cohort of LEN + ETP + IFM in patients with relapsed or refractory OS (NCT02432274).

METHODS

- This is a phase 1/2, multicenter, open-label trial conducted in 5 cohorts (**Figure 1**).

Figure 1. Study Design



- LEN was administered daily and continuously throughout all treatment cohorts.
  - For the combination treatment, IFM (3000 mg/m² IV QD for 3 days) + ETP (100 mg/m² IV QD for 3 days) was administered on days 1–3 of each 21-day cycle, for a total of 5 cycles.
- Tumor assessments were performed by the investigators per Response Evaluation Criteria In Solid Tumors (RECIST) version (v)1.1.

RESULTS

Baseline Characteristics

- At data cutoff (March 30, 2018), 30 patients were enrolled in the single-agent expansion cohort and 18 patients were enrolled in the ongoing combination dose-finding cohort (LEN 11 mg/m²: n = 7; LEN 14 mg/m²: n = 11) (**Table 1**).
  - Patients in the single-agent expansion cohort were more heavily pretreated prior to enrollment compared with patients in the combination cohort.
  - 30 (100%) Patients in the single-agent cohort had metastatic disease at presentation vs 17 (94.4%) patients in the combination cohort.

Table 1. Patient Baseline Characteristics

Parameter	Phase 2 LEN (n = 30)	LEN + ETP + IFM (n = 18)
Age group, n (%)		
≥ 2 to < 6 years	0	1 (5.6)
≥ 6 to < 18 years	23 (76.7)	13 (72.2)
≥ 18 to ≤ 25 years	7 (23.3)	4 (22.2)
Sex ratio, male/female	13/17	13/5
Median body surface area, m² (range)	1.6 (0.9–2.1)	1.6 (0.8–2.1)
Median body mass index, kg/m² (range)	20.5 (12.5–41.5)	19.5 (11.4–36.9)
Lansky or Karnofsky scores, n (%)		
60	1 (3.3)	0
70	2 (6.7)	3 (16.7)
80	5 (16.7)	5 (27.8)
90	15 (50.0)	3 (16.7)
100	7 (23.3)	7 (38.9)
Prior anticancer therapy regimens, n (%)		
0	0	0
1	7 (23.3)	10 (55.6)
2	14 (46.7)	4 (22.2)
≥ 3	9 (30.0)	4 (22.2)
Prior VEGF-targeted therapy, n (%)		
Bevacizumab	1 (3.3)	0
Pazopanib	2 (6.7)	0

ETP, etoposide; IFM, ifosfamide; LEN, lenvatinib; VEGF, vascular endothelial growth factor.

Efficacy

- Efficacy outcomes are summarized in **Table 2**.
- It is important to note that this is an ongoing study.
  - Patients are still undergoing treatment, including several patients who have achieved a response (**Figure 2** and **Figure 3**).
  - Therefore, the efficacy data have not yet fully matured.

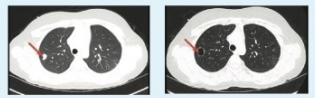
Table 2. Efficacy Outcomes per Investigator Assessment, as Measured by RECIST v1.1

Parameter	Phase 2 LEN (n = 30)	LEN + ETP + IFM (n = 18)
Patients evaluable for PFS-4, n*	27	17
PFS-4, n (%)	9 (33.3)	10 (58.8)
95% CI	16.5–54.0	32.9–81.6
Patients with measurable disease, n	26	16
BOR, n (%)		
CR	0	0
PR	2 (7.7)	2 (12.5)
SD	15 (57.7)	11 (68.8)
PD	9 (34.6)	3 (18.8)
ORR, n (%)	2 (7.7)	2 (12.5)
95% CI	0.9–25.1	1.6–38.3
Median DOR, months† (95% CI)	4.6 (NE–NE)	NE (NE–NE)
Median PFS, months (95% CI)	3.4 (1.8–6.5)	13.1 (4.6–NE)
Median follow-up time for PFS, months (95% CI)	5.5 (3.7–12.9)	7.4 (4.2–8.4)
Patients who had anticancer surgery during study treatment, n (%)	3 (10.0)	5 (27.8)

*PFS-4 evaluable patients include those who are alive and free of disease progression at 4 months from the first dose, and exclude those who discontinued the study due to adverse events or for other reasons than disease progression or death.
†For patients with CR or PR.
BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; ETP, etoposide; IFM, ifosfamide; LEN, lenvatinib; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PFS-4, progression-free survival at 4 months; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors, version 1.1; SD, stable disease.

- For the combination cohort, the median follow-up time for PFS was 7.4 months (95% confidence interval [CI], 4.2–8.4 months).
  - 10 Patients (58.8%) achieved PFS at 4 months (PFS-4), with a median PFS of 13.1 months.
- An example of patient response is shown in **Figure 2**, which illustrates the evolution from a solid pulmonary lesion at baseline to a hollow cyst structure after 2 cycles of LEN 11 mg/m² + ETP+ IFM.

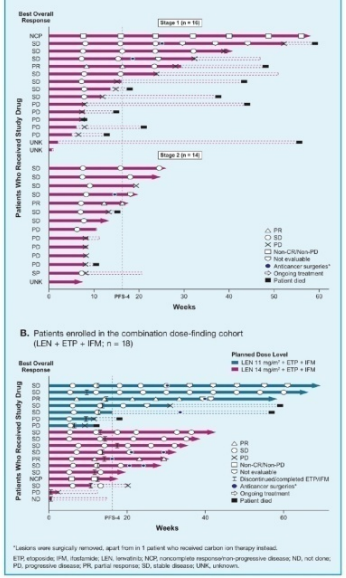
Figure 2. Example of Patient Imaging Outcome



Baseline | 2 Cycles of LEN + EPT + IFM

ETP, etoposide; IFM, ifosfamide; LEN, lenvatinib.

Figure 3. Duration of Treatment and Response



*Lesions were surgically removed, apart from in 1 patient who received carbon ion therapy instead.
ETP, etoposide; IFM, ifosfamide; LEN, lenvatinib; NCP, noncomplete response/non-progressive disease; ND, not done; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.

Safety

- The extent of exposure is described in **Table 3**.

Table 3. Extent of Exposure

Parameter	Phase 2 LEN (n = 30)	LEN 11 mg/m² + ETP + IFM (n = 7)	LEN 14 mg/m² + ETP + IFM (n = 11)
Treatment duration, days, median (range)	LEN: 83.5 (5–407)	LEN: 216.0 (63–486)	LEN: 200.0 (4–298)
Number of cycles received, median (range)	LEN: 3.5 (1–15)	LEN: 10.0 (3–23) IFM: 5.0 (3–5) ETP: 5.0 (3–5)	LEN: 9.0 (1–15) IFM: 5.0 (1–6) ETP: 5.0 (1–6)
Percent of intended dose, mean (range)	LEN: 91.7 (47–103)	LEN: 85.3 (66–102) IFM: 96.2 (79–102) ETP: 94.8 (78–103)	LEN: 87.8 (56–104) IFM: 97.7 (83–104) ETP: 97.7 (83–103)

ETP, etoposide; IFM, ifosfamide; LEN, lenvatinib.

- In the combination cohort, dose-limiting toxicities (DLTs) were reported in 1 patient receiving LEN 11 mg/m² + ETP + IFM and 2 patients receiving LEN 14 mg/m² + ETP + IFM (**Table 4**).
  - 6 Additional patients will be treated at LEN 14 mg/m² + ETP + IFM, because 1 patient experienced a hematologic DLT and 1 patient experienced nonhematologic DLTs, as per protocol.

Table 4. Dose-limiting Toxicities

Dose cohort	Patient	Dose-limiting toxicity	Grade*
LEN 11 mg/m² + ETP + IFM	1	Thrombocytopenia	4
LEN 14 mg/m² + ETP + IFM	2	Epistaxis	3
		Thrombocytopenia	4
	3†	Oral dysesthesia	2
		Lower back pain	2
		Muscle spasms / body cramps	3

*Worst grade reported.
†For Patient 3, the 3 adverse events cumulatively caused dose interruption or reduction, which resulted in administration of < 75% of the planned LEN dosage in Cycle 1.
ETP, etoposide; IFM, ifosfamide; LEN, lenvatinib.

- An overview of safety for the combination cohort by dose level and the single-agent cohort are summarized in **Table 5**.

Table 5. Summary of TEAEs

Parameter, n (%)	Phase 2 LEN (n = 30)	LEN 11 mg/m² + ETP + IFM (n = 7)	LEN 14 mg/m² + ETP + IFM (n = 11)
TEAEs	28 (93.3)	7 (100.0)	11 (100.0)
Treatment-related TEAEs	27 (90.0)	7 (100.0)	11 (100.0)
TEAEs with CTCAE grade ≥ 3	19 (63.3)	6 (85.7)	10 (90.9)
Serious TEAEs **Fatal TEAEs**	19 (63.3) 3 (10.0)	5 (71.4) 1 (14.3)	8 (72.7) 0
TEAEs leading to study drug withdrawal / discontinuation	3 (10.0)	0	1 (9.1)
TEAEs leading to study drug dose reduction	6 (20.0)	5 (71.4)	4 (36.4)
TEAEs leading to study drug interruption	16 (53.3)	5 (71.4)	8 (72.7)

CTCAE, Common Terminology Criteria for Adverse Events; ETP, etoposide; IFM, ifosfamide; LEN, lenvatinib; TEAE, treatment-emergent adverse event.

- The 1 fatal treatment-emergent adverse event (TEAE) in the combination cohort was dyspnea (n = 1), and was considered related to disease progression, as per investigator assessment.
- The 3 fatal TEAEs in the single-agent cohort were respiratory failure (n = 1) and cardiorespiratory arrest (n = 2), and were considered related to disease progression as per investigator assessment.
- The most common TEAEs for the single-agent cohort and the combination cohort are presented in **Table 6** and **Table 7**, respectively.
- Notably, several TEAEs were common to both the single-agent and combination cohorts including nausea, diarrhea, hypothyroidism, and hypertension.
  - TEAEs that were more common in the combination included anemia, thrombocytopenia, neutropenia, and stomatitis.

Table 6. Common TEAEs* in the Single-agent Expansion Cohort

Preferred term, n (%)	LEN 14 mg/m² (n = 30)	
	Any Grade	Grade ≥ 3
Headache	13 (43.3)	1 (3.3)
Hypothyroidism	13 (43.3)	0
Vomiting	13 (43.3)	0
Decreased appetite	12 (40.0)	2 (6.7)
Diarrhea	12 (40.0)	1 (3.3)
Proteinuria	12 (40.0)	1 (3.3)
Increased blood thyroid-stimulating hormone concentrations	11 (36.7)	0
Hypertension	11 (36.7)	1 (3.3)
Asthenia	10 (33.3)	1 (3.3)
Back pain	10 (33.3)	4 (13.3)
Constipation	10 (33.3)	0
Musculoskeletal pain	10 (33.3)	2 (6.7)
Pyrexia	10 (33.3)	0
Abdominal pain	9 (30.0)	1 (3.3)
Arthralgia	9 (30.0)	1 (3.3)
Fatigue	9 (30.0)	0
Nausea	9 (30.0)	0
Extremity pain	9 (30.0)	0
Decreased weight	9 (30.0)	1 (3.3)
Cough	8 (26.7)	0
Dyspnea	8 (26.7)	2 (6.7)
Dysphonia	6 (20.0)	0

*TEAEs are classified as common if they occur at any grade in ≥ 20% of the total number of patients.
LEN, lenvatinib; OS, osteosarcoma; TEAEs, treatment-emergent adverse events.

Table 7. Common TEAEs* for the Combination Dose-finding Cohort

Preferred term, n (%)	LEN 11 mg/m² + ETP + IFM (n = 7)		LEN 14 mg/m² + ETP + IFM (n = 11)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nausea	5 (71.4)	0	9 (81.8)	0
Diarrhea	6 (85.7)	3 (42.9)	6 (54.5)	1 (9.1)
Vomiting	5 (71.4)	0	7 (63.6)	1 (9.1)
Anemia	7 (100.0)	5 (71.4)	4 (36.4)	3 (27.3)
Abdominal pain	4 (57.1)	1 (14.3)	5 (45.5)	0
Arthralgia	2 (28.6)	0	7 (63.6)	0
Stomatitis	3 (42.9)	1 (14.3)	6 (54.5)	2 (18.2)
Back pain	4 (57.1)	1 (14.3)	4 (36.4)	0
Epistaxis	4 (57.1)	2 (28.6)	4 (36.4)	2 (18.2)
Headache	3 (42.9)	0	5 (45.5)	0
Neutropenia	4 (57.1)	3 (42.9)	4 (36.4)	4 (36.4)
Thrombocytopenia	3 (42.9)	3 (42.9)	5 (45.5)	4 (36.4)
Constipation	4 (57.1)	0	3 (27.3)	0
Febrile neutropenia	4 (57.1)	4 (57.1)	3 (27.3)	3 (27.3)
Hypothyroidism	1 (14.3)	0	6 (54.5)	0
Extremity pain	4 (57.1)	1 (14.3)	3 (27.3)	0
Pyrexia	3 (42.9)	0	4 (36.4)	0
Decreased weight	4 (57.1)	0	3 (27.3)	0
Decreased appetite	3 (42.9)	0	3 (27.3)	0
Fatigue	2 (28.6)	0	4 (36.4)	0
Hypertension	1 (14.3)	0	4 (36.4)	0
Hypokalemia	4 (57.1)	2 (28.6)	1 (9.1)	0
Hypophosphatemia	3 (42.9)	3 (42.9)	2 (18.2)	1 (9.1)
Decreased platelet count	2 (28.6)	2 (28.6)	3 (27.3)	3 (27.3)
Proteinuria	3 (42.9)	1 (14.3)	2 (18.2)	0
Cough	0	0	4 (36.4)	0
Dry skin	2 (28.6)	0	2 (18.2)	0
Hematuria	2 (28.6)	0	2 (18.2)	0
Oral pain	2 (28.6)	0	2 (18.2)	0
Oropharyngeal pain	2 (28.6)	0	2 (18.2)	0
Rash	0	0	4 (36.4)	0
Sinus bradycardia	0	0	4 (36.4)	0

*TEAEs are classified as common if they occur at any grade in ≥ 20% of the total number of patients.
ETP, etoposide; IFM, ifosfamide; LEN, lenvatinib; TEAE, treatment-emergent adverse event.

- The incidence of pneumothorax was 16.7% in the single-agent cohort, and 11.1% in the combination cohort.

CONCLUSIONS

- The preliminary results from this ongoing study suggest that LEN has activity in patients with relapsed/refractory OS.
  - Because this study is ongoing, longer follow-up is needed for the efficacy data to fully mature.
- 9 Patients (33.3%) treated with LEN monotherapy (14 mg/m²) achieved PFS-4, and 2 patients (7.7%) achieved partial responses.
- 5 Patients (27.8%) in the combination dose-finding OS cohort and 3 patients (10%) in the single-agent expansion OS cohort had lesions surgically resected, which is the ultimate goal of treatment in relapsed and refractory OS.
- LEN + ETP + IFM combination therapy had a manageable safety profile.
  - There were no unexpected toxicities—grade 3 and 4 thrombocytopenia and febrile neutropenia are toxicities typically associated with chemotherapy regimens.
  - Toxicities that were attributable to LEN were manageable with dose interruptions and reductions.
- The incidence of pneumothorax (11%–17%) in this study of patients with OS and aged 2 to ≤ 25 years is higher than that seen in previous studies of LEN monotherapy in adults (~ 0.9%).[5,7]

References

1. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology, Version 2: Bone Cancer*; 2018.
2. Xie L et al. *Oncol Rep*. 2017;38:625-636.
3. Lenvima® (lenvatinib) [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2017.
4. Matsuki M et al. Poster presented at: AACR Annual Meeting; April 16–20, 2016; New Orleans, LA. #3265.
5. Gaspar N et al. ASCO Annual Meeting; June 2–6, 2017; Chicago, IL.
6. Schlumberger M et al. *N Engl J Med*. 2015;372:621-630.
7. Kudo M et al. *Lancet*. 2018;391:1163-1173.

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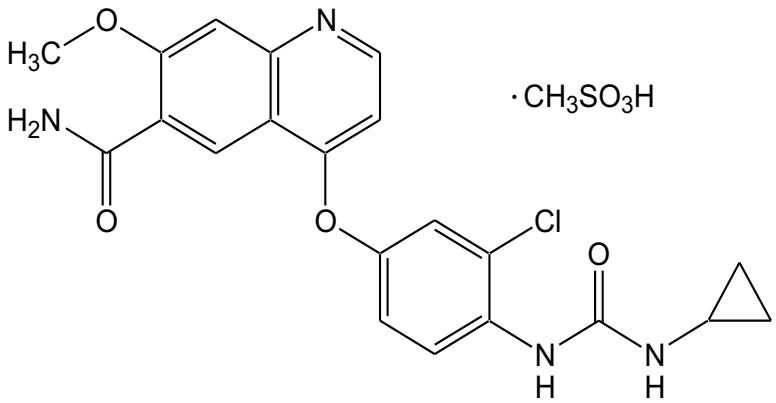
ClinicalTrials.gov identifier: NCT02432274

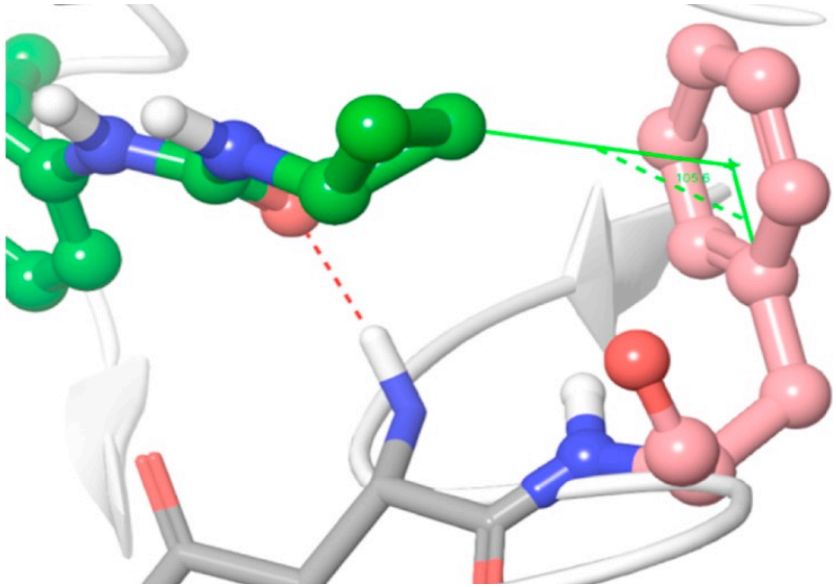
Lenvatinib

» Chemical name: 4-[3-Chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6- carboxamide methanesulfonate

» An oral ATP-binding/competitive small-molecule tyrosine kinase inhibitor and prevents ligand induced receptor auto-phosphorylation

» Targets: **VEGFR1-3, FGFR1-4, PDGFR, RET and c-KIT**

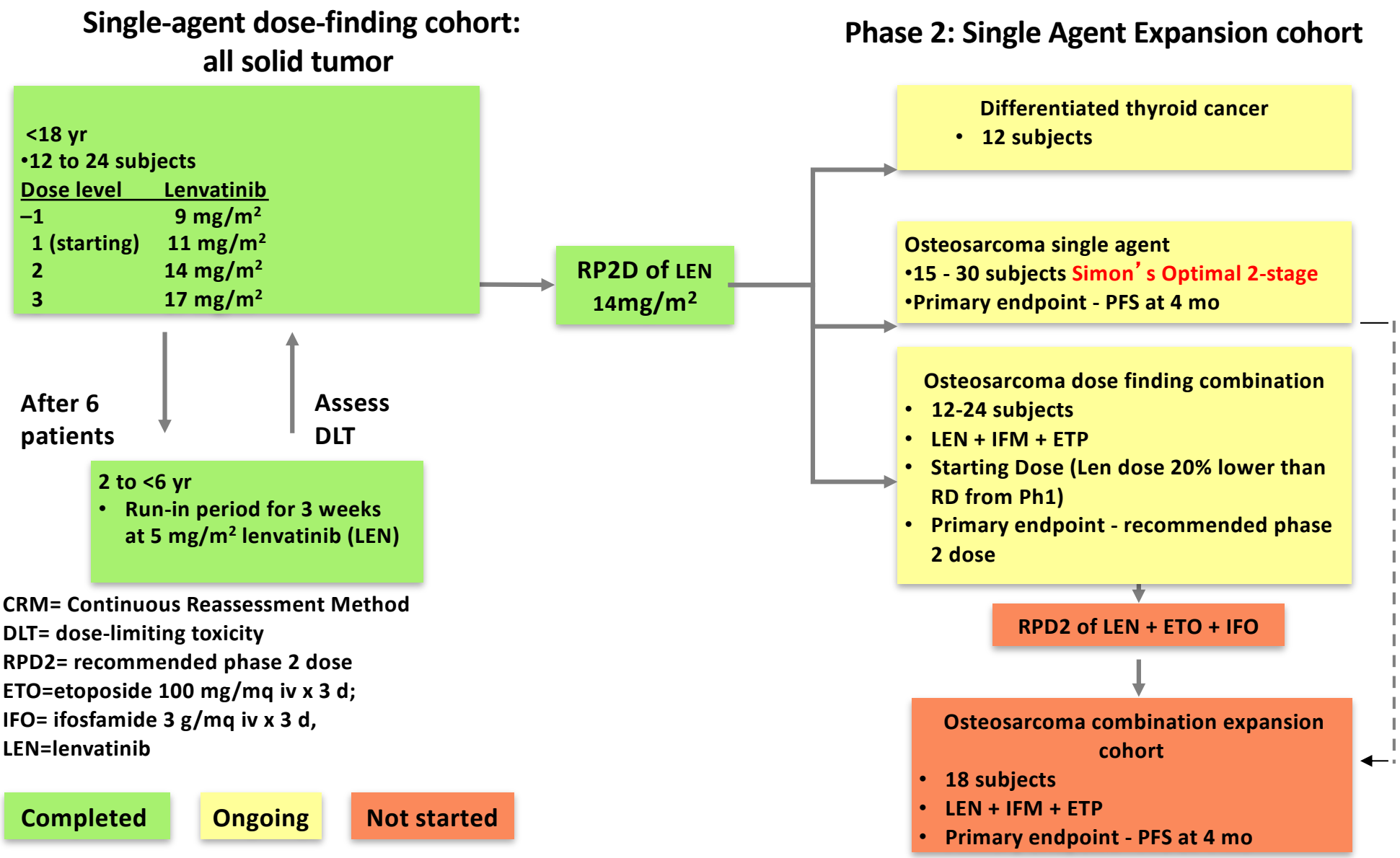




Okamoto K et al, ACS Med. Chem. Lett, 2014

Cortesia C. Meazza

Study Design



It is important to note that this is an ongoing study.

- Patients are still undergoing treatment, including several patients who have achieved a response (**Figure 2** and **Figure 3**).
- Therefore, the efficacy data have not yet fully matured.

Table 2. Efficacy Outcomes per Investigator Assessment, as Measured by RECIST v1.1

Parameter	Phase 2 LEN (n = 30)	LEN + ETP + IFM (n = 18)
Patients evaluable for PFS-4, n*	**27**	**17**
PFS-4, n (%)	9 (33.3)	10 (58.8)
95% CI	16.5–54.0	32.9–81.6
Patients with measurable disease, n	**26**	**16**
BOR, n (%)		
CR	0	0
PR	2 (7.7)	2 (12.5)
SD	15 (57.7)	11 (68.8)
PD	9 (34.6)	3 (18.8)
ORR, n (%)	2 (7.7)	2 (12.5)
95% CI	0.9–25.1	1.6–38.3
Median DOR, months† (95% CI)	4.6 (NE–NE)	NE (NE–NE)
Median PFS, months (95% CI)	3.4 (1.8–6.5)	13.1 (4.6–NE)
Median follow-up time for PFS, months (95% CI)	5.5 (3.7–12.9)	7.4 (4.2–8.4)
Patients who had anticancer surgery during study treatment, n (%)	3 (10.0)	5 (27.8)

*PFS-4 evaluable patients include those who are alive and free of disease progression at 4 months from the first dose, and exclude those who discontinued the study due to adverse events or for other reasons than disease progression or death.

†For patients with CR or PR.

BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; ETP, etoposide; IFM, ifosfamide; LEN, lenvatinib; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PFS-4, progression-free survival at 4 months; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors, version 1.1; SD, stable disease.

For the combination cohort, the median follow-up time for PFS was 7.4 months (95% confidence interval [CI], 4.2–8.4 months).

- 10 Patients (58.8%) achieved PFS at 4 months (PFS-4), with a median PFS of 13.1 months.

CONCLUSIONS

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#11520

Apatinib for advanced osteosarcoma after failure of standard multimodal therapy: An open label phase 2 clinical trial.

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PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: EMANUELA PALMERINI

#11520
Apatinib for advanced osteogenic sarcoma after failure of standard multimodal therapy: An open label phase 2 clinical trial

- Apatinib (oral TKI VEGFR-2) 750 mg once daily for body surface area (BSA) ≥ 1.5 and 500 mg daily for BSA < 1.5
- Phase II
- Relapse or unresectable OGS prior therapy
- Primary Endpoint
  - Objective Response Rate (CR + PR at least 3 months + PFS at 4 Mo)

> 16 years

About Apatinib

Table 1: Comparison of common anti-angiogenic TKIs with different median inhibition concentrations (IC_{50})

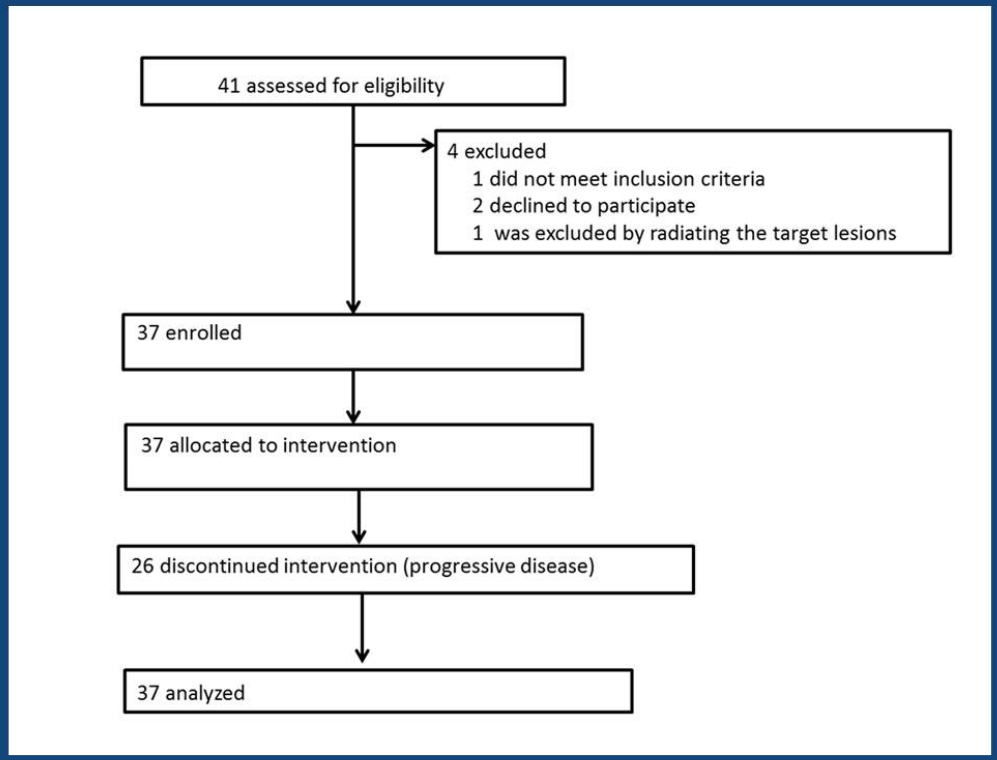
Target	IC_{50}[1]			
	Apatinib	Sorafenib	Sunitinib	Pazopanib
VEGFR-1	70	--	2	10
VEGFR-2	2	90	10	30
VEGFR-3	--	--	17	47
PDGFR-β	537	--	8	84
c-kit	420	68	--	74
FGFR-1	>10000	580	--	--
FLT-3	--	58	--	--

[1]Median inhibition concentration: concentration that reduces the effect by 50%.

Outcome Measures

- Primary Outcome Measures
  - Progression-free survival, PFS at 4 months
  - Objective response rate, ORR
- Secondary Outcome Measures
  - Clinical benefit rate, CBR at 6 months
  - Duration of response, DOR
  - Overall survival, OS
  - Toxicity (CTCAE version 4.03)
  - Quality of life (EORTC QLQ-C30 (V3.0))

Procedures



Apatinib 750 mg once daily for body surface area (BSA) ≥ 1.5 and 500 mg daily for BSA < 1.5;

For this study design, the first time point for evaluation was set at **one month (almost 4 weeks)**;

If CR/PR appears according to RECIST 1.1, the next evaluation would be conducted 4 weeks later to confirm this PR;

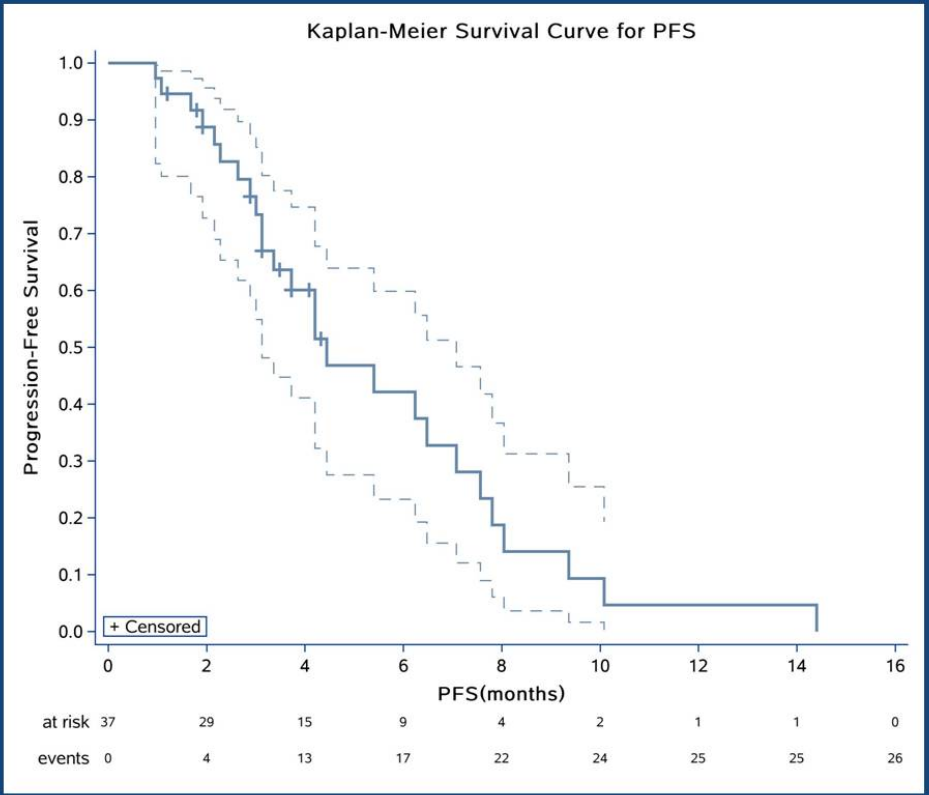
If SD appears, the next evaluation would be conducted 8 weeks later to confirm this SD;

The evaluation would be repeated every two months thereafter.

Outcomes

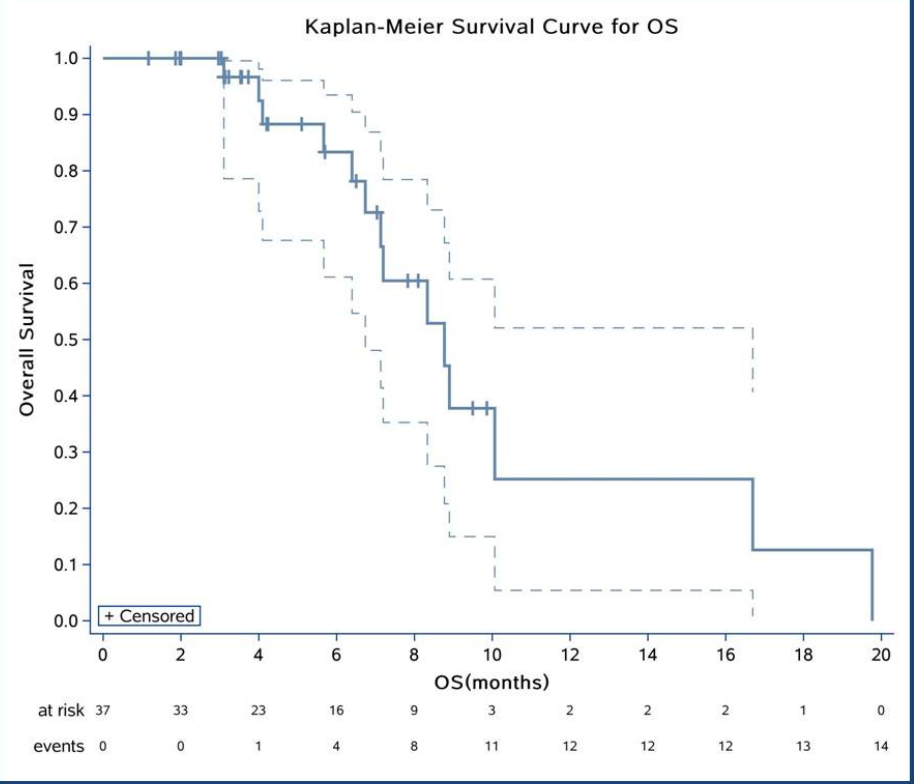
Best overall response	N(%)	95% CI
CR	0 (0.00%)	
PR	16 (43.24%)	
SD	8 (21.62%)	
PD	13 (35.14%)	
duration of response, DOR (months) (N=16)	5.07 m	(2.70,6.53) m
ORR (CR+PR)	16 (43.24%)	(27.1%, 60.5%)
CBR (CR+PR+SD at least 6 months)	13 (35.14%)	(20.21%, 52.54%)

PFS



	result
N	37(100.00%)
Median PFS (95% CI) month	4.50(3.47,6.27)
Q1:Q3	3.13 : 6.63
PFS at 4 months	56.75%(39.43%, 70.84%)
PFS at 6 months	36.77%(21.48%, 52.16%)

OS



	result
N	37(100.00%)
Median OS (95% CI) month	9.87(7.97,18.93)
Q1:Q3	7.27 : 20.20

Adverse Event That Occurred in At Least One Patient

Adverse event	All (%)	Grade 1(%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Sum of all	33(89·19%)	27(72·97%)	28(75·68%)	9(51·35%)	10(27·03%)

Apatinib adverse event

Grade 3-4 adverse events (%):

- Pneumothorax 6 (16.2)
- Wound dehiscence 4 (10.8)
- Proteinuria 3 (8.1)
- Diarrhea 3 (8.1)

#11520 Apatinib (TKI) for OGS

- Promising treatment for OGS
- PFS at 4 months is very encouraging
- Toxicities are common will need to be managed
- Other TKI

Pazopanib and oral topotecan

Mark Agulnik, Nisha Anjali Mohindra, Mohammed M. Milhem, Steven Attia, Steven Ian Robinson, Alfred Rademaker, Susan E. Abbinanti, Rasima Cehic, Catherine Humphreys, Bethany Prudner, Scott H. Okuno, Brian Andrew Van Tine

- »3 cohorts STS non-Lipo, osteosarcoma, liposarcoma
- »≥ 18 years
- »pazopanib 800mg oral daily
- »topotecan 8mg orally day 1, 8, 15 on a 28-day cycle

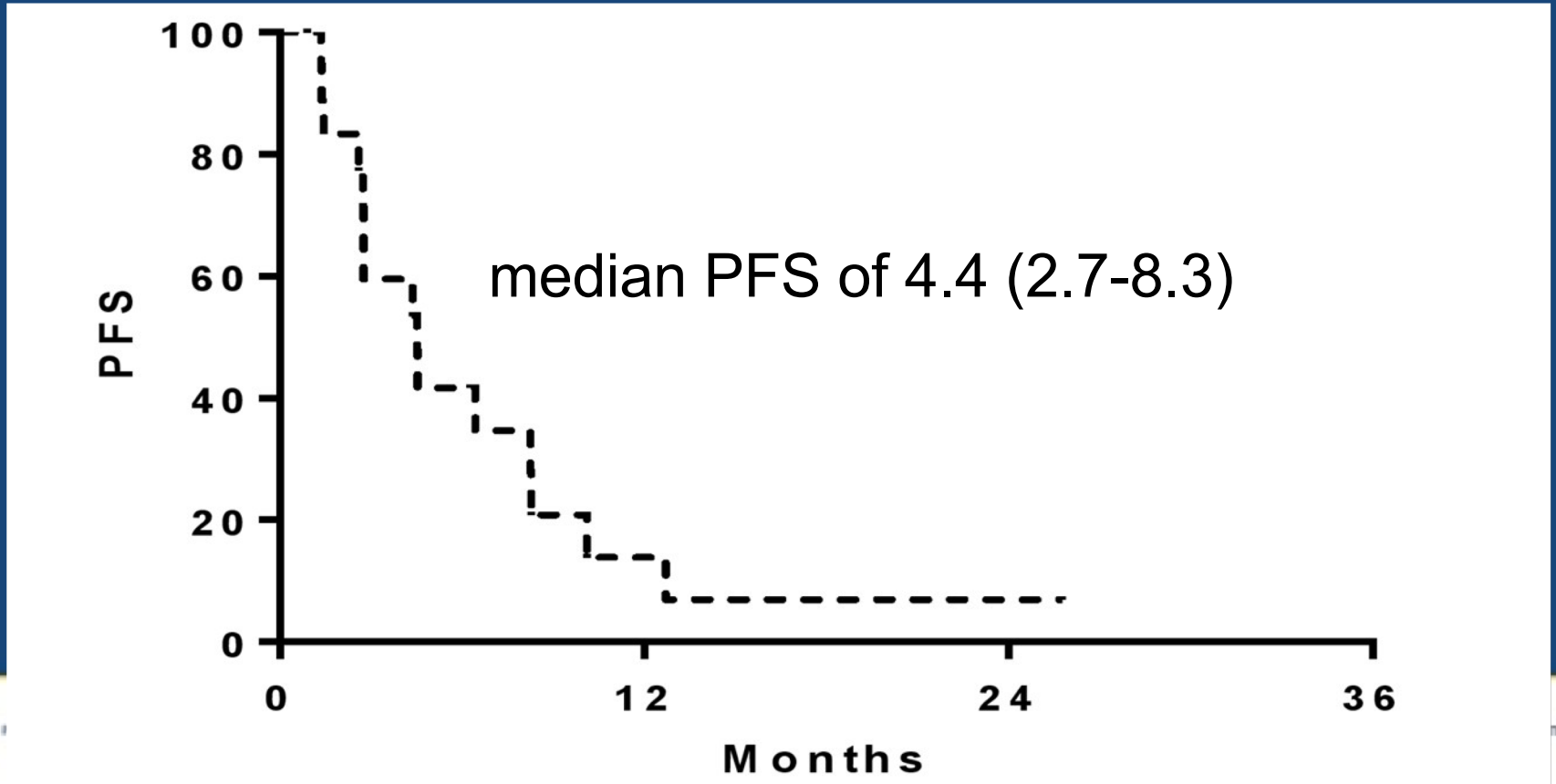
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY:

Pazopanib and oral topotecan

Characteristic Frequency (%)	Cohort 1 (n=104)	Cohort 2 (n=21)	Cohort 3 (n=19)
Age- Median (Range)	55.5 (24-80)	40.5 (18-71)	57.2 (32-77)
Male Female	38 (36.5) 66 (63.5)	11 (52.4) 10 (47.6)	13 (68.4) 6 (31.6)
ECOG PS 0 1	 48 (46.1) 56 (53.8)	 11 (52.3) 10 (47.6)	 8 (42.1) 11 (57.8)
Histology	**STS-non liposarcoma**	**Osteosarcoma**	**Liposarcoma**
Number of prior treatments 1 2 3 4	 43 (41.3) 35 (33.7) 18 (17.3) 8 (7.7)	 5 (23.8) 9 (42.8) 7 (33.3) 0	 13 (68.4) 3 (15.8) 3 (15.8) 0

Pazopanib and oral topotecan



PFS Cohort 2: Osteosarcoma

Pazopanib and oral topotecan

	Cohort 1 (n=104)	Cohort 2 (n=21)	Cohort 3 (n=19)
Median PFS (95% CI)	4.4 months (2.8 m - 6.1 m)	4.5 months (2.7 m - 8.3 m)	1.4 months (1.1 m -4.4 m)
# Patients Alive and PF at 12 weeks	51 out of 90 (56.6%)	10 out of 17 (58.8%)	7 out of 18 (38.8%)
Best Response CR PR SD	 1 (1%) 6 (6.6%) 60 (66%)	 0 1 (5%) 16 (80%)	 0 0 8 (44.4%)
CBR (CR+PR+SD)	**67** **74.4%**	**17** **85%**	**8** **44.4%**
Median OS (95% CI)	11.1 months (7.2m-17.8m)	11.1 months (6.3m-19.1m)	12.8 months (3.3m-25.3m)

Pazopanib and oral topotecan

Grade 3-4 adverse events (%):

neutropenia	(42)
thrombocytopenia	(29)
hypertension	(16)
anemia	(12)

Pazopanib and oral topotecan

Conclusions

STS: same as pazopanib monotherapy, more toxic

Osteosarcoma: extremely promising and cohort 2 will be expanded.

Liposarcoma: ineffective

Poster 056 3042722

SCREENING OF SYNERGISTIC REAGENT WITH PAZOPANIB AGAINST OSTEOSARCOMA USING COMPOUND LIBRARY.

Yuki Yada[2]; *Kunihiro Asanuma*[1]; *Koji Kita*[1]; *Tomohito Hagi*[1]; *Tomoki Nakamura*[1]; *Akihiro Sudo*[1]

[1]*Mie University, Yokkaichi, Mie, Japan;* [2]*Mie Prefectural general Medical Center, Yokkaichi, Japan*

- Japan, preclinico
- Combinazione PZB con crizotinib notevole effetto antiproliferativo

Conclusion: In this study, the combination therapy of PZP and CRZ showed a remarkable anti-proliferative effect against OS cells.From the western blot analysis, this combination therapy inhibited tumor growth by inducing apoptosis and interrupting cell cycle progression.
PZP and CRZ combination therapy may inhibit tumor progression in the clinical situation and to create a new inhibitor for c-kit, PDGFR, and ALK may have synergistic effect for OS treatment. This needs further study.

Phase 1 Multicenter Trial to Assess the Maximum Tolerated Dose, Safety, Pharmacokinetics, and Pharmacodynamics of Pazopanib in Combination with Irinotecan and Temozolomide (PAZIT) for Children and Young Adults with Advanced Sarcoma

University of California San Francisco

Kieuhoa T. Vo[1], Jennifer G. Michlitsch[2], Avanthi T. Shah[1], Janel Long-Boyle[3], Mi-Ok Kim[4], W. Clay G
E. Alejandro Sweet-Cordero[1], Katherine K. Matthay[1], Steven G. DuBois[5]

Departments of [1]Pediatrics, [3]Clinical Pharmacy, and [4]Epidemiology and Biostatistics, University of California, San Francisco School of Medicine, UCSF Benioff
San Francisco, CA, USA; [2]Department of Pediatrics, UCSF Benioff Children's Hospital, Oakland, CA, USA; [5]Dana-Farber/Boston Children's Cancer and Blood D
Harvard Medical School, Boston, MA, USA

Abstract

BACKGROUND: Sarcomas express pro-angiogenic factors that may represent therapeutic targets. Pazopanib, an oral multi-kinase inhibitor of VEGFR-(1-3), c-kit, and PDGFR, is FDA-approved for the treatment of advanced soft tissue sarcomas. In a phase 1 study of single-agent pazopanib in children with recurrent or refractory solid tumors, this agent was well tolerated and the clinical activity was encouraging in this heavily pre-treated population. Preclinical studies have demonstrated a potential additive or synergistic interaction between anti-angiogenic agents and cytotoxic chemotherapy. The combination of irinotecan and temozolomide is well tolerated and provides a modest degree of antitumor activity in heavily pre-treated sarcoma patients, thus making it a useful platform onto which new compounds may be tested.

METHODS: This is a phase 1, open-label, multicenter trial of pazopanib in combination with irinotecan and temozolomide (PAZIT) in children and young adults ages 6-30 years with relapsed or refractory sarcomas (NCT03139331). The primary objectives are to determine the recommended phase 2 dose, describe toxicities, and describe pharmacokinetic parameters in this population. Secondary and exploratory objectives include evaluation of disease response and exploration of pharmacodynamic effects of PAZIT. Pazopanib is administered orally on days 1-21 of 21-day cycles according to assigned dose level. All patients receive fixed doses of irinotecan IV (50 mg/m^2/day) or PO (90 mg/m^2/day) and temozolomide 100 mg/m^2/day PO on days 1-5. Oral cephalosporin diarrhea prophylaxis is required. Dose escalation follows a standard 3+3 design evaluating up to three pazopanib dose levels. Following dose escalation, up to 10 additional patients will be enrolled to the dose expansion cohort to obtain additional toxicity and efficacy data. Correlative studies include changes in plasma angiogenic factors and circulating tumor DNA. Enrollment began in May 2017 and is ongoing.

Objectives

Primary Objectives

- To determine the recommended phase 2 dose (RP2D) of pazopanib combined with irinotecan and temozolomide (PAZIT) in patients with relapsed/ refractory sarcoma.
- To describe the toxicities of the combination of PAZIT in this population.

Secondary Objectives

- To preliminarily define the anti-tumor activity within the confines of a phase 1 study.
- To describe the pharmacokinetics of pazopanib and irinotecan.

Exploratory Objectives

- To evaluate pharmacodynamic effects of PAZIT using plasma angiogenic factors and circulating tumor DNA.

Background

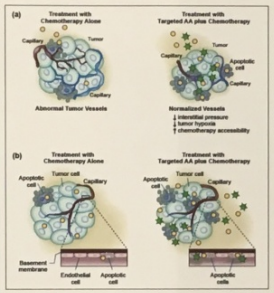


Figure 1. Proposed biological mechanisms supporting combination anti-angiogenic approaches in sarcoma, including: (a) transient "normalization" of the abnormal tumor vasculature by anti-angiogenic agents resulting in improved blood perfusion and enhanced chemotherapy accessibility and antitumor activity; (b) synergistic interaction of combination therapy leads to enhanced direct cytotoxicity of tumor cells and/or endothelial cells.

Vo KT, Matthay KK, DuBois SG. Clin Sarcoma Res 2016.

- Pazopanib is an oral, multi-kinase VEGFR-(1-3), c-kit, and PDGFR inhibitor; approved by FDA and EMA for treatment of advanced soft-tissue sarcoma in adults
  - Children's Oncology Group phase 1 study of single-agent pazopanib established pediatric RP2D (450 mg/m^2/day)
- Irinotecan and temozolomide is a well-tolerated regimen and has modest activity in advanced sarcoma, thus making it a useful platform onto which new agents may be added

Clinical Experience

Only study of pazopanib combined with irinotecan and temozolomide.

Study Design

Phase 1, open-label study of PAZIT with dose escalation (3+3 design) and dose expansion cohorts

Companion Studies

1. Optional pharmacokinetic and pharmacodynamic (plasma VEGF, VEGFR2, and endoglin) testing
2. Optional genomic analysis of cell-free DNA and/or somatic mutations in circulating tumor DNA in plasma

Treatment Schema

Pazopanib (PO daily per nomo	
Dose Level	**Pediatric Dose**
-1	225 mg/m^2
1 (start)	350 mg/m^2
2	450 mg/m^2
Irinotecan 50 mg/m^2/day IV on D cycle 1; 50 mg/m^2/day IV or 90 m Days 1-5 during subsequent cycle	
Temozolomide 100 mg/m^2/day P	
Cephalosporin diarrhea prophyla	

Key Eligibility

- Age ≥ 6 and ≤ 30 years of age
- BSA ≥ 0.7 m^2 AND able to swallow whole tablets
- Relapsed or refractory EWS/peripheral PNET, OS, RMS, non-RMS, DSRCT
- Standard performance score, recovery time from prior therapies, and organ function requirements
- Standard exclusion criteria associated with anti-angiogenic therapies
- No previous treatment with pazopanib
- Previous treatment with irinotecan and/or temozolomide allowed if no documentation of disease progression on these agents

Participating Centers

UCSF Benioff Children's Hospitals
Oakland | San Francisco

DANA-FARBER Boston Children's
CANCER AND BLOOD DISORDERS CENTER

Treatment Schema

Pazopanib (PO daily per nomogram, Days 1-21)		
Dose Level	**Pediatric Dose**	**Adult Dose (Max)**
-1	225 mg/m^2	400 mg
1 (start)	350 mg/m^2	600 mg
2	450 mg/m^2	800 mg

Irinotecan 50 mg/m^2/day IV on Days 1-5 during cycle 1; 50 mg/m^2/day IV or 90 mg/m^2/day PO on Days 1-5 during subsequent cycles

Temozolomide 100 mg/m^2/day PO on Days 1-5

Cephalosporin diarrhea prophylaxis on Days -1 to 8

Paper 042 3042857

CABOZANTINIB IN PATIENTS WITH ADVANCED OSTEOSARCOMAS AND EWING SARCOMAS: A FRENCH SARCOMA GROUP (FSG)/ US NATIONAL CANCER INSTITUTE PHASE II COLLABORATIVE STUDY

Antoine Italiano[1]; *Nicolas Penel*[2]; *Emmanuelle Bompas*[3]; *Sophie Piperno-Neumann*[4]; *Marina Pulido*[1]; *Natacha Entz-Werle*[5]; *Axel Le Cesne*[6]; *Christine Chevreau*[7]; *Florence Duffaud*[8]; *Isabelle Ray-Coquard*[9]; *Maud Toulmonde*[1]; *Carine Bellera*[1]; *Jean-Yves Blay*[9]

[1]*Institut Bergonié, Bordeaux, France;* [2]*Centre Oscar Lambret, Lille, France;* [3]*Institut Cancerologie de l'Ouest, Nantes, France;* [4]*Institut Curie, Paris, France;* [5]*CHU de Strasbourg, Strasbourg, France;* [6]*Institut Gustave Roussy, Villejuif, France;* [7]*Oncopole Toulouse, Toulouse, France;* [8]*APHM Marseille, Marseille, France;* [9]*Centre Leon Berard, Lyon, France*

Results: As of 06/2018, 88 patients (45 OS + 43 ES) have been included. 55.6% of patients had 3 or more previous lines of treatment. At the time of interim statistical analysis, 34 patients with OS and 23 patients with ES were eligible and evaluable for the first endpoint after central histological and radiological review. 18 OS pts (52.9%) had tumor shrinkage resulting in partial response in 6 cases (17.6%) and stable disease in 12 cases (35.3%). 12 patients (35.3%) were progression-free at 6 months. 16 ES (69.6%) had tumor shrinkage resulting in partial response in 5 cases (21.7%) and stable disease in 11 cases (47.8%). 7 (30.4%) patients were progression-free at 6 months. Cabozantinib reached the primary endpoint to justify continuing accrual for both strata. 19 patients are still on treatment.

Conclusion: Cabozantinib shows significant activity in patients with advanced OS and ES sarcomas. Final efficacy, safety and translational data will be presented at the meeting.

Conclusions

What PFS is an appropriate endpoint for ostesarcoma trial?

- 50% 6moPFS OS (Grignani G, Lancet Oncol 2015)
- 40% 6mo PFS STS (van Glabbeckè, Eur J Cnacer 2002)

Cortesia E Palmerini

Response to TKI in osteosarcoma

Regorafenib + BSC	Lenvatinib/LEN+IFO+ETO	Apatinib	Pazopanib + Topotecan	Sorafenib	Sorafenib + Everolimus
11504 ASCO 2018 Oral	11527 ASCO 2018	11520 ASCO 2018 Oral	162173 ASCO 2018 Oral	Ann. Oncology 2012	Lancet Oncology 2015
26	27/17	37	21 Pt	35	38
8%RR	8%/13% RR	43%RR	5% RR	14%RR	10%RR
16 w mPFS	3.4/13.1 mo mPFS	4.5 mo mPFS	4.4 mo mPFS	4 mo mPFS	5 mo mPFS
35% PFS at 24w	33%/59 at 4 mo	37% PFS 6 mo	59% PFS at 12 w	46% PFS at 4 mo	45% PFS at 6mo
OS 50% at 12mo		OS 28% at 12mo	mOS 11 mo	OS 25% at 12mo	OS 40% at 12 mo

Annals of Oncology 23: 508–516, 2012
doi:10.1093/annonc/mdr151
Published online 28 April 2011

A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study

G. Grignani[1]*, E. Palmerini[2], P. Dileo[3], S. D. Asaftei[4], L. D'Ambrosio[1], Y. Pignochino[1], M. Mercuri[5], P. Picci[6], F. Fagioli[4], P. G. Casali[3], S. Ferrari[2] & M. Aglietta[1]

[1]Medical Oncology Unit, Institute for Cancer Research and Treatment, Candiolo; [2]Chemotherapy Unit, Department of Musculoskeletal Oncology, Istituti Ortopedici Rizzoli, Bologna; [3]Sarcoma Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [4]Department of Pediatric Oncology, Ospedale Infantile Regina Margherita, Torino; [5]5th Department of Orthopedics, Istituti Ortopedici Rizzoli and University of Bologna, Bologna; [6]Laboratory of Experimental Oncology, Istituti Ortopedici Rizzoli, Bologna, Italy

Results: Thirty-five patients were enrolled. PFS at 4 months was 46% (95% CI 28% to 63%). Median PFS and OS were 4 (95% CI 2–5) and 7 (95% CI 7–8) months, respectively. The CBR was 29% (95% CI 13% to 44%). We observed 3 (8%) partial responses (PRs), 2 (6%) minor responses (<30% tumor shrinkage) and 12 (34%) stable diseases (SDs). For six patients (17%), PR/SD lasted ≥6 months. Noteworthy, tumor density reduction and [^{18}F]2-fluoro-2-deoxy-D-glucose–positron emission tomography responses were observed among SD patients. Sorafenib was reduced or briefly interrupted in 16 (46%) patients and permanently discontinued in one (3%) case due to toxicity.

Conclusions: Sorafenib demonstrated activity as a second- or third-line treatment in terms of PFS at 4 months with some unprecedented long-lasting responses. Sorafenib, the first targeted therapy showing activity in osteosarcoma patients, deserves further investigations.

Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial

Giovanni Grignani, Emanuela Palmerini, Virginia Ferraresi, Lorenzo D'Ambrosio, Rossella Bertulli, Sebastian Dorin Asaftei, Angela Tamburini, Ymera Pignochino, Dario Sangiolo, Emanuela Marchesi, Federica Capozzi, Roberto Biagini, Marco Gambarotti, Franca Fagioli, Paolo Giovanni Casali, Piero Picci, Stefano Ferrari, Massimo Aglietta, for the Italian Sarcoma Group

Lancet Oncol 2015; 16: 98–107
Published Online December 11, 2014
http://dx.doi.org/10.1016/S1470-2045(14)71136-2

See Comment page 12

Medical Oncology, Candiolo Cancer Institute-FPO, IRCCS, Candiolo, D Sangio hemother Onc Ortopec Italy (E Palmerini MD, E Marchesi PhD, S Ferrari MD); Medical Oncology A, IRCCS Regina Elena National Cancer Institute, Rome, Italy (V Ferraresi MD); Department of Oncology, University of Torino, Turin, Italy (L D'Ambrosio, Y Pignochino, D Sangiolo, Capozzi, Prof M Aglietta); Adult Mesenchymal Tumor Medical Oncology Unit, Fondazione CCS Istituto Nazionale Tumori, Milan, Italy (R Bertulli MD, P G Casali MD); Pediatric Onco-ematology, Città della Salute e

Summary

Background Results of previous study showed promising but short-lived activity of sorafenib in the treatment of patients with unresectable advanced and metastatic osteosarcoma. This treatment failure has been attributed to the mTOR pathway and might therefore be overcome with the addition of mTOR inhibitors. We aimed to investigate the activity of sorafenib in combination with everolimus in patients with inoperable high-grade osteosarcoma progressing after standard treatment.

Methods We did this non-randomised phase 2 trial in three Italian Sarcoma Group centres. We enrolled adults platin, a day urvival 4.

Interpretation Although the combination of sorafenib and everolimus showed activity as a further-line treatment for patients with advanced or unresectable osteosarcoma, it did not attain the prespecified target of 6 month PFS of 50% or greater.

s were 5%) of 38 patients and permanent discontinuation for two (5%) patients. The most common grade 3–4 adverse events were lymphopenia and hypophosphataemia each in six (16%) patients, hand and foot syndrome in five (13%), thrombocytopenia in four (11%), and fatigue, oral mucositis, diarrhoea, and anaemia each in two (5%). One patient (3%) had a grade 3 pneumothorax that required trans-thoracic drainage, and that recurred at the time of disease progression. This was reported as a serious adverse event related to the study drugs in both instances. No other serious adverse events were reported during the trial. There were no treatment-related deaths.

Interpretation Although the combination of sorafenib and everolimus showed activity as a further-line treatment for patients with advanced or unresectable osteosarcoma, it did not attain the prespecified target of 6 month PFS of 50% or greater.

Funding Italian Sarcoma Group.

Drug repurposing in osteosarcoma

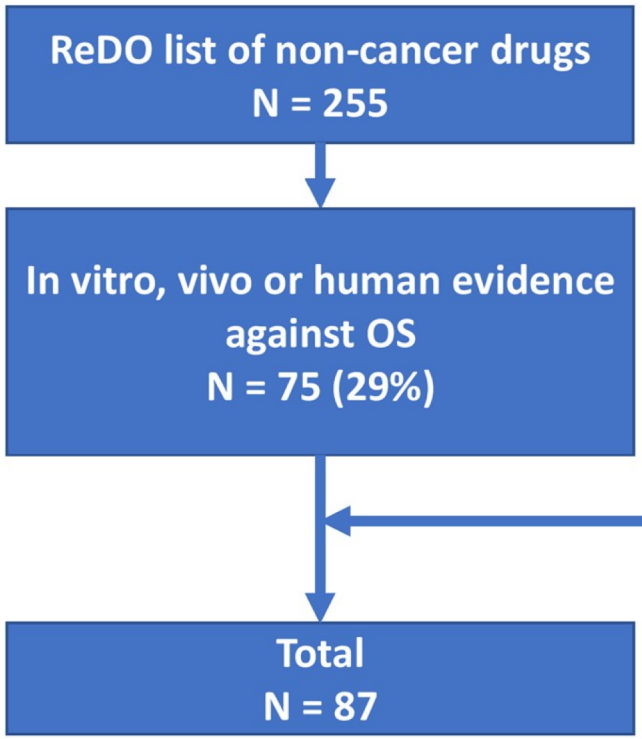
Gauthier Bouche, Pan Pantziarka; The Anticancer Fund, Strombeek-Bever, Belgium

- An alternative development pathway that seeks to reuse existing drugs as the source of new treatment options
- Pubmed search:

list of 240 approved non-cancer drugs AND osteosarcoma

Drug repurposing in osteosarcoma

Results



- **Of the 255 ReDO drugs, 75 (29%) had at least one** human activity against OS.
- We have **not yet fully quantified the number of re** **approved for other cancers**, which also represents for future trials. We **currently have found 12 of th**
- **Combining both ReDO and non-OS cancer drugs,** grouped them according to their mechanisms of a

Drug repurposing in osteosarcoma

MoA Category	Drug *(main indication)*	Type of evidence
Cell differentiation	Calcitriol *(vitamin D deficiency)*	Animal model
	All-trans retinoic acid *(APL)*	Case report / Animal model
Cytotoxicity & potentiation of chemotherapy	Simvastatin *(hypercholesterolemia)*	Animal model
	Glucocorticoids *(inflammation)*	Animal model
	Caffeine *(infant apnea)*	Human trial / Animal model
	Esomeprazole *(peptic ulcer)*	Human trial / Animal model
	Verapamil *(hypertension)*	Case reports / In vitro
	Piroxicam *(osteoarthritis)*	Canine trials / Animal model
Stem cells cytotoxicty	Metformin *(type 2 diabetes)*	Animal model
	Disulfiram *(alcohol dependency)*	In vitro
Immunomodulation	Sirolimus *(prevention organ rejection)*	Human trial / Animal model
	Thalidomide *(multiple myeloma)*	Case report / Animal model
Epigenetic modifications	Decitabine *(AML)*	Animal model
	Valproic acid *(epilepsy)*	Animal model
	Vorinostat *(T-cell lymphoma)*	Animal model
Cell-cell interaction	Aspirin *(CVD prevention)*	Animal model
	Heparin *(VTE)*	Animal model
	Warfarin *(embolisation)*	Human trial / Animal model
	Plerixafor *(stem cell mobilization)*	Animal model

immunomodulator

Poster 075 3042651

THE EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON OSTEOSARCOMA CELLS

Joseph Elsissy[1]; Lee M. Zuckerman[1]; Nadine L. Williams[1]; Troy G. Shields[1]; Saied Mirshahidi[2]

[1]Orthopaedic Surgery, Loma Linda University Medical Center, Loma Linda, CA, USA; [2]Biospecimen Laboratory, Loma Linda University Medical Center, Loma Linda, CA, USA

- USA, preclinico
- Ketorolac e indometacina inducono apoptosi in cell OS nel topo

Conclusions

Drug repurposing: COFFE + ASPIRIN

miglior risposta dopo una sbronza…

..e anche
per l'osteosarcoma?

...grazie

..e..

Luca Coccoli
UO Oncoematologia Pediatrica
AOUP Pisa Dir. G Casazza
CROP Toscana Dir. C. Favre
lucacoccoli@ao-pisa.toscana.it

XXII RIUNIONE ANNUALE ITALIAN SARCOMA GROUP Pisa, 4-5-6 aprile 2019

La città di Pisa è lieta di ospitare la XXIII Riunione Annuale dell'Italian Sarcoma Group, importante evento scientifico-culturale di confronto multidisciplinare fra i vari specialisti esperti della cura dei sarcomi (anatomo patologi, chirurghi, radiologi, radioterapisti, oncologi medici, psicologi, biologi....) al fine di approfondire la conoscenza, di analizzare i protocolli di studio attualmente in uso e di discutere circa nuove soluzioni diagnostiche e terapeutiche in tale campo.

La Sessione Educazionale del primo giorno avrà come obiettivo la divulgazione del sapere su queste neoplasie soprattutto fra i medici in formazione e gli specializzandi che rappresentano il futuro dell'Associazione e ai quali è doveroso trasmettere lo stesso orgoglio di appartenenza.

Ampio spazio verrà dedicato alle Associazioni di pazienti perché una diagnosi di sarcoma non ha solo ricadute fisiche e psicologiche sulla persona: ci sono conseguenze pratiche, logistiche, economiche e giuridiche, che il paziente deve conoscere per gestire al meglio il proprio percorso di guarigione e la rete di relazioni personali e professionali al fine di mantenere una qualità di vita rispettosa della dignità umana e della sua routine familiare

Ti invitiamo a prendere parte all'evento perché anche la tua partecipazione è fondamentale per il proseguo del commino intrapreso da ISG.

Arrivederci a Pisa

Rodolfo Capanna

PROGRAMMA

4 aprile 2019	
14:00 18:00	Sessione Educazionale

5 aprile 2019	
08:30 18:00	Sessioni Scientifiche
20:30	Cena Sociale

6 aprile 2019	
08:00 13:00	Sessioni Scientifiche

SEDE
San Ranieri Hotel Pisa
Via Filippo Mazzei, 2 – Pisa

ISCRIZIONE
L'iscrizione è gratuita previa registrazione OBBLIGATORIA. Per iscriversi è necessario compilare la Scheda di Iscrizione presente nel sito:
http://www.italiansarcomagroup.org/
ed inviarla via mail o fax alla segreteria organizzativa, che confermerà le iscrizioni accettate.

CENA SOCIALE 5 aprile 2019
L'iscrizione alla Cena Sociale è gratuita previa registrazione OBBLIGATORIA. Per iscriversi è necessario compilare la Scheda di Iscrizione presente nel sito:
http://www.italiansarcomagroup.org/
ed inviarla via mail o fax alla segreteria organizzativa, che confermerà le iscrizioni accettate.

SEGRETERIA ORGANIZZATIVA AdArte EVENTI

Via G. di Vittorio 2 – 40057 Cadriano di Granarolo E. (BO)
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HOTEL
La Segreteria Organizzativa, ha opzionato camere presso la sede del Congresso a tariffe convenzionate.

- **Camera DUS Superior** *colazione inclusa*
€ 120,00 IVA inclusa a camera al giorno
- **Camera Doppia Superior** *colazione inclusa*
€ 130,00 IVA inclusa a camera al giorno

Suggeriamo di effettuare la prenotazione alberghiera con ampio anticipo.
Per effettuare la prenotazione alberghiera è necessario compilare la Scheda di Iscrizione presente nel sito:
http://www.italiansarcomagroup.org/
ed inviarla via e-mail o fax alla segreteria organizzativa, che confermerà la prenotazione in base alla disponibilità.

ECM – Educazione Continua in Medicina
L'evento sarà accreditato ECM dal Provider MED3

per le seguenti figure professionali:
Psicologi, Biologi, Farmacisti, Medici (tutte le discipline) ed Infermieri.
Obiettivi formativi tecnico professionali della Riunione sono: Linee guida, Protocolli e Procedure

Cod. VIII_03 - Stampato Novembre 2018

..arrivederci a Pisa e..

32ND ANNUAL MEETING OF THE
EUROPEAN MUSCULO SKELETAL ONCOLOGY SOCIETY
20TH EMSOS NURSE AND ALLIED PROFESSIONS GROUP MEETING

FLORENCE ITALY - MAY 15 - 17 2019

PROGRAMME

MAIN TOPICS

New Technologies in Orthopaedic Oncology

New drugs in Sarcoma Therapy: new agents, target therapies, immunotherapy

New drugs in Tumor Like disease

New strategies in Radiationtherapy

Advances in Imaging Technology

Computer assisted surgery and Robotics

Custom-Made Prosthesis and Devices

Patient Specific Instruments

Paediatric Orthopaedic Oncology

Lenghtening prostheses and devices

Spine and Sacral Tumors

Infections: new strategies in prevention and treatment

Implant coatings

Mininvasive Thera pies in Orthopaed ic O ncology

New devices after amputations

"Salvage of Limb Salvage"

..di nuovo a Firenze!