METZOLIMOS Metronomic Cyclophosphamide (CP) and Methotrexate (MTX) combined with Zoledronic Acid (ZA) and Sirolimus (SIR) in patients with advanced Solid Tumor with bone metastasis and advanced pretreated Osteosarcoma (OSS) A Phase Ib Study

Maud Toulmonde[1], Perrine Marec-Berard[2], Cyril Lervat[3], Coralie Cantarel[1], Emilie Toulza[1], Sabrina Sellan-Albert[1], Sophie Cousin[1], Kevin Bourcier[1], Mariella Spalato-Ceruso[1], Raul Perret[1], Simone Mathoulin-Pelissier[1], Jean-Yves Blay[2], Nicolas Penel[3], Carine Bellera[1] and **Antoine Italiano[1]**

[1]Institut Bergonié, Bordeaux, France; [2]Centre Léon Bérard, Lyon, France; [3]Centre Oscar Lambret, Lille, France

INTRODUCTION

- Advanced pretreated OSS has a very poor prognosis [1].
- Metronomic CP and MTX, as well as mTOR inhibitors have shown little activity in pediatric cancers including OSS [2-6].
- Preclinical data suggest that ZA could have a synergic effect when combined with mTOR inhibition in OSS [7-9].

PATIENTS and METHODS

Design

- A prospective phase Ib study investigating the combination of SIR with CP, MTX and ZA.
→ Part I = A dose-escalation phase (3 + 3 design) in patients ≥ 18 years with bone metastatic solid tumors.
→ Part II = An expansion cohort dedicated to patients ≥ 13 years with advanced pretreated OSS.

Treatment

- SIR was given at two dose levels (4 mg and 6 mg) continuously, in combination with :
- CP 50 mg x 2 per day, 1 week on / 1 week off,
- MTX at 2.5 mg x 2 per day, on day 1 and day 4, every week,
- and ZA 4mg IV every 4 weeks.

Methods - Endpoints

- Primary endpoints were :
- dose limiting toxicities (DLT), maximum tolerated dose and recommended phase II dose (RP2D) of SIR combined with CP, MTX and ZA for part I,
- and 6-month non-progression rate according to RECIST v1.1 for part II.

- Secondary endpoints included :
- Safety,
- Six-month objective response rate (ORR),
- One-year progression-free (PFS) and overall survivals (OS),
- And pharmacodynamics biomarker analyses.

- At least one non-progression at 6 months after centralized review of imaging was needed among 14 patients to consider activity of the combination.

RESULTS

Flow Chart and Patients Characteristics

From February 2015 to March 2021, 23 patients were included in the three participating centers, nine in part I and 14 in part II (**Figure 1**). Patients characteristics are described in **Table 1**.

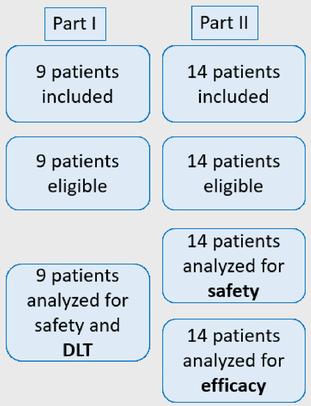

Figure 1. Flow Chart

	Part I (N = 9)		Part II (N = 14)	
	n	%	n	%
Sex				
Male	3	33	8	57
Female	6	67	6	43
ECOG				
0	6	67	4	29
1	3	33	10	71
Median age at diagnosis, years (min-max)	54	(37-73)	27	(14-80)
Tumour type				
Breast carcinoma	5	56		
Prostate carcinoma	3	33		
Cholangiocarcinoma	1	11		
Osteosarcoma			14	100
Median number of chemotherapy lines (min-max)	4	(3-8)	1	(1-3)

Table 1. Patients Characteristics

- In part I, **nine patients** with breast (56%), prostate (33%) or biliary duct carcinoma (11%) were included.

Median number of cycles was 2 (1-6).
Two DLT were reported at dose level 2:
- one grade 3 neutropenia
- one grade 3 anemia

Therefore, dose level 1 (4mg SIR) was the RP2D for part II.

- In part II, **14 OSS patients** were included.

Median age was 27 years (14 - 80).
Median number of previous lines in the advanced disease was 1 (1-3).

At the time of analysis, 11 patients had died. Reason for study discontinuation was progressive disease for 10 patients (72%), toxicity for two (14%) (one grade 2 platelet count decrease and one grade 5 unrelated lung infection), and investigator decision for two (14%), including one for cryotherapy of a residual lesion after an excellent partial response.

Safety

Overall, 64 adverse events related to study drugs were reported, of which 14 (22%) grade 3, and 2 grade 4 (3%).
They were mainly asthenia, nausea, mucositis oral, anemia, lymphocyte and platelet count decrease (**Table 2**).

	Grade 1-2		Grade 3		Grade 4	
	n	%	n	%	n	%
Fatigue	4	29				
Nausea	4	29				
Diarrhea	2	14	1	7		
Mucositis oral	6	43				
Anemia	3	21	2	14		
Platelet count decreased	5	36	2	14		
Neutrophil count decreased	1	7	1	7		
Lymphocyte count decreased	2	14	4	29	2	14
ALAT increased	2	14	1	7		
ASAT increased	1	7	1	7		
GGT increased			1	7		
Hypophosphatemia			1	7		

Table 2. Number of patients with > one grade 1 adverse event related to the treatment, by intensity (n = 14)

Efficacy

- Median follow up was 27.5 months [95% CI : 12.8-27.5].
- Two non-progressions at 6 months (14%) were observed, including a partial response (7%).
- One-year PFS was 21.4% [95%CI 5.2-44.8].
- Median OS was 12.8 months [95% CI : 2.8-20.4].

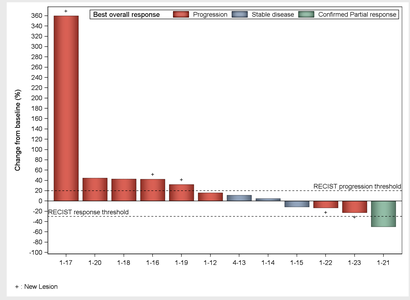

Figure 2. Waterfall plots of tumor shrinkage (n = 12)

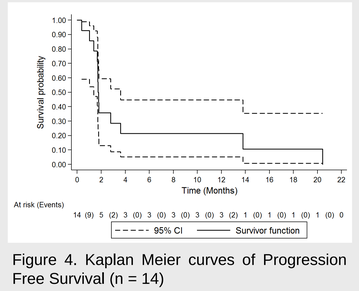

Figure 4. Kaplan Meier curves of Progression Free Survival (n = 14)

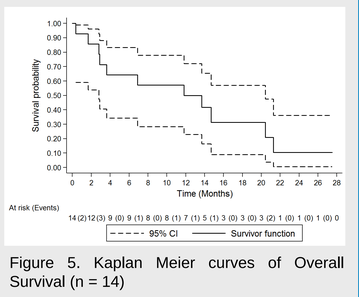

Figure 5. Kaplan Meier curves of Overall Survival (n = 14)

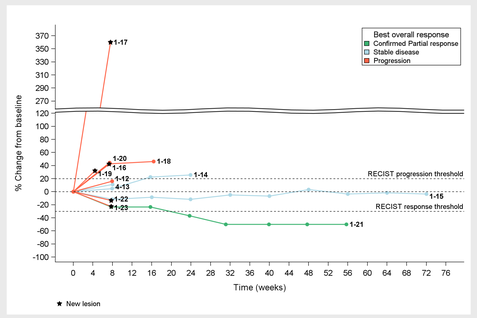

Figure 3. Spider plots of treatment duration (n = 12)

- There was no significant correlation between dosage of sirolimus plasma level at either Cycle 1-day 9, Cycle 1-day 18 or Cycle 2-day 1 and occurrence of grade 3-4 toxicity, or tumor shrinkage.

- Ancillary proteomics analyses are ongoing on plasma samples.

CONCLUSION

This study shows that successfully conducting joint pediatric and adult early phase trials in rare cancers is feasible.
The combination of SIR at 4 mg daily with CP, MTX and ZA has an acceptable toxicity profile and reached the initial targeted efficacy rate in advanced pretreated OSS patients.
Further analyses are needed to understand which patients may benefit from this approach.

This study was registered with ClinicalTrial.gov, number NCT02517918. This study was partly funded by a grant from Anticancer Funds and performed with an institutional support from Pfizer.

REFERENCES

[1] Gelderblom H, et al. Survival after recurrent osteosarcoma: data from 3 European Osteosarcoma Intergroup (EOI) randomized controlled trials. Eur J Cancer 2011
[2] Penel N, et al. Cyclophosphamide-based metronomic chemotherapy: after 10 years of experience, where do we stand and where are we going? Crit Rev Oncol Hematol 2012
[3] Petrilli AS, et al. Preliminary safety and outcome report of the metronomic therapy from the Latin American osteosarcoma treatment protocol 2006. J Clin Oncol 2011
[4] Pignochino Y, et al. The Combination of Sorafenib and Everolimus Abrogates mTORC1 and mTORC2 upregulation in osteosarcoma preclinical models. Clin Cancer Res 2013
[5] Houghton PJ, et al. Stage 2 combination testing of rapamycin with cytotoxic agents by the Pediatric Preclinical Testing Program. Mol Cancer Ther 2010
[6] Chawla SP, et al. Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas. J Clin Oncol 2012
[7] Dass CR, Choong PF. Zoledronic acid inhibits osteosarcoma growth in an orthotopic model. Mol Cancer Ther 2007
[8] Ory B, et al. Zoledronic acid suppresses lung metastases and prolongs overall survival of osteosarcoma-bearing mice. Cancer 2005
[9] Moriceau G, et al. Zoledronic acid potentiates mTOR inhibition and abolishes the resistance of osteosarcoma cells to RAD001 (Everolimus): pivotal role of the prenylation process. Cancer Res 2010