MYXOID / ROUND CELL LIPOSARCOMA

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DISCLOSURE SLIDE

I have the following financial relationship to disclose:

- I have acted as consultant and participated to Advisory Board Meetings of Pharma Mar, Madrid, Spain

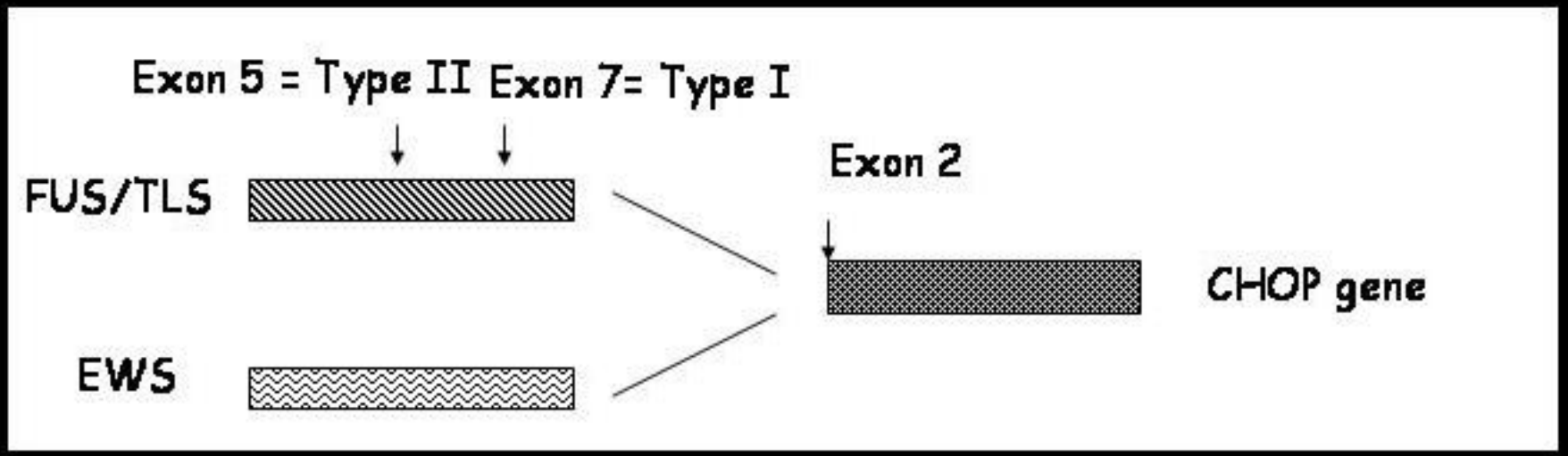
THE DISEASE

FUS/TLS-CHOP

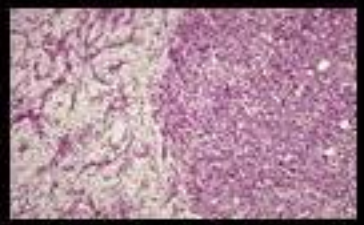
t(12;16)(q13;p11)

EWS-CHOP

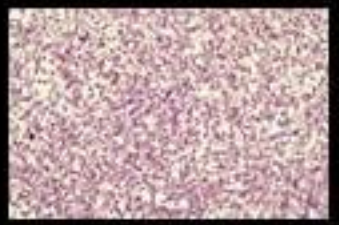
t(12;22)(q13;q12)



Pure myxoid



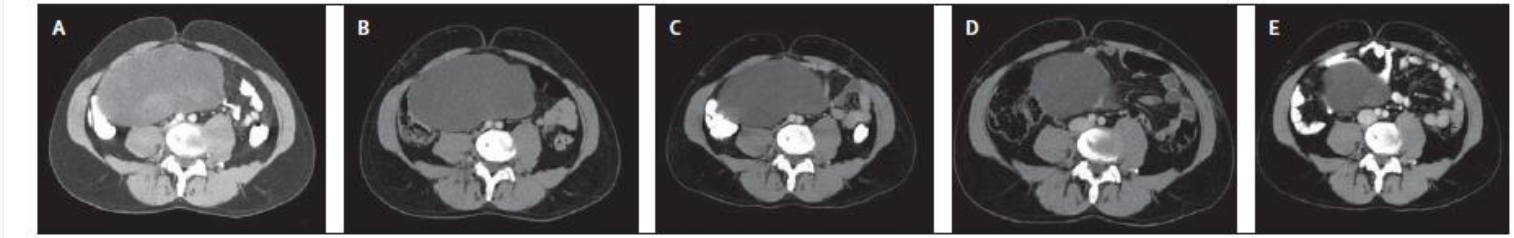
Myxoid /round cells

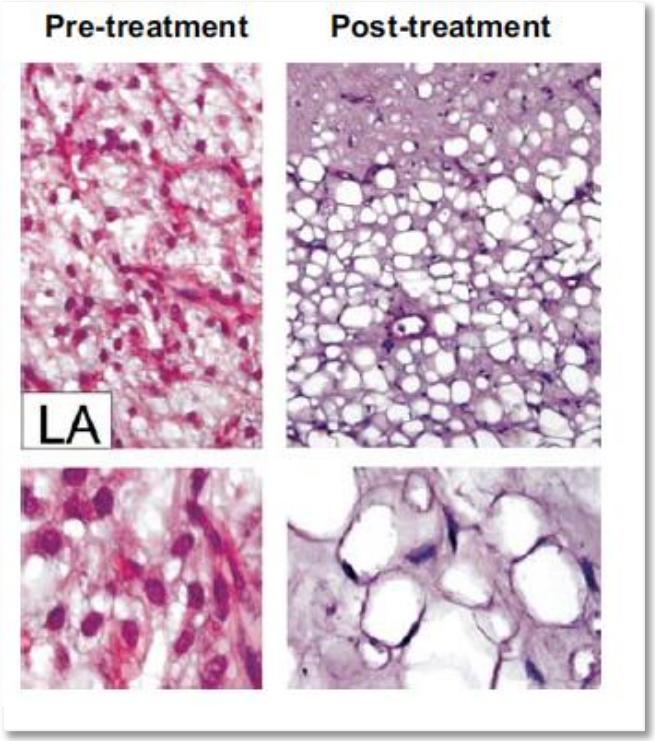


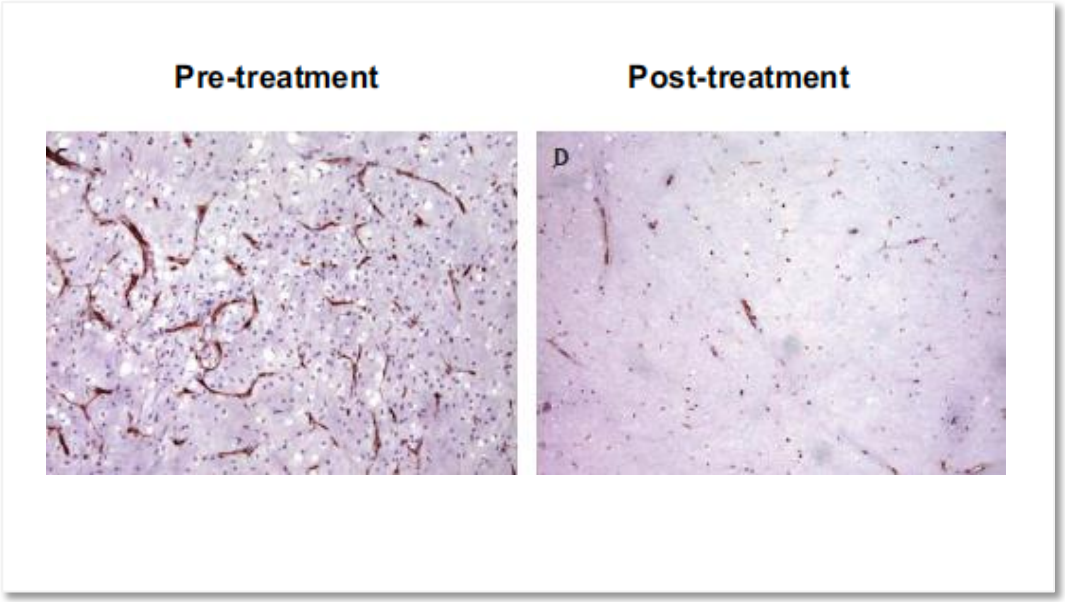
Round cells

TRABECTEDIN PROMOTES DIFFERENTIATION AND REGRESSION OF CAPILLARY NETWORKS IN MYXOID LIPOSARCOMA TUMORS

t(12;16)(q13;p11) => FUS/CHOP







Grosso, Lancet Oncol, 2007; Forni, Mol Cancer Ther 2009

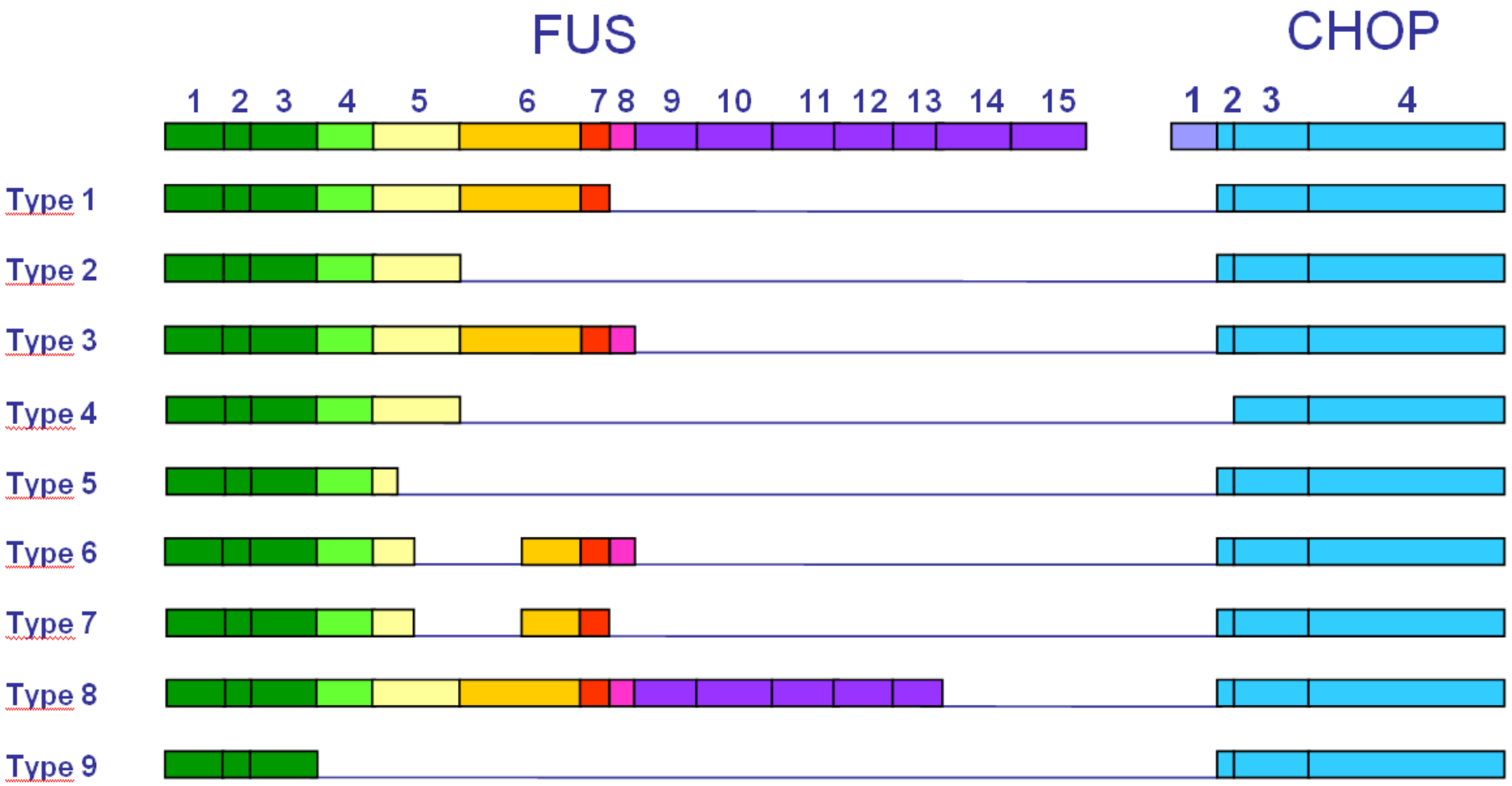
ACTIVITY OF TRABECTEDIN IN STS vs MLS

	all	MLS
No. Pts	189	51
OR	8%	50%
PFS @6mos	20%	88%
Median PFS, mos	3	14

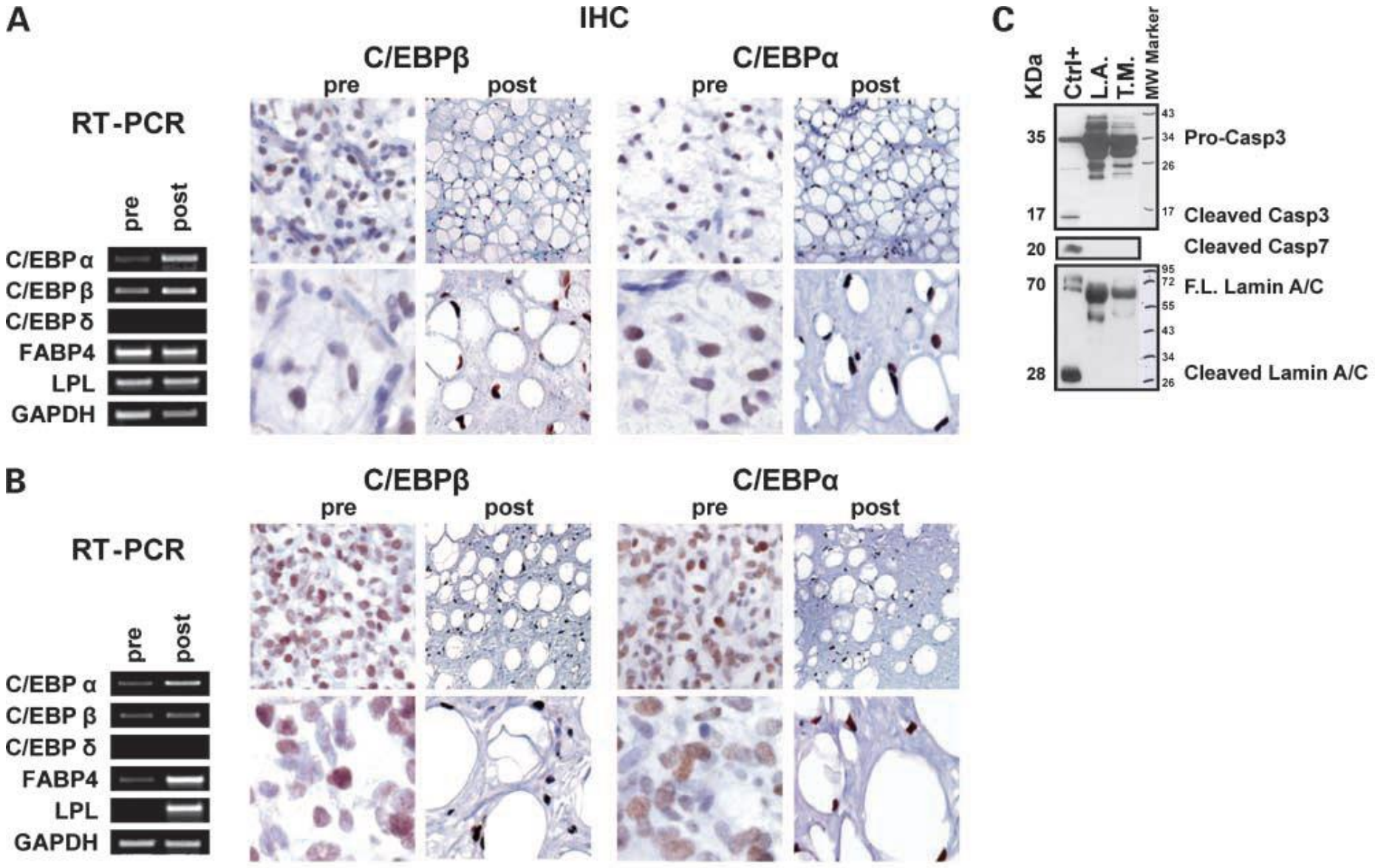
F Grosso et al, Lancet Oncology, 8: 595-602 (2007)

FUS-CHOP
t(12;16)(q13; p11)
~ 95%

EWS-CHOP
t(12;22)(q13; q12)



Biochemical and Biophysical Research Communications **279,** 838–845 (2000)


A
IHC
C/EBPβ
C/EBPα
pre
post
pre
post
RT-PCR
pre
post
C/EBP α
C/EBP β
C/EBP δ
FABP4
LPL
GAPDH
B
C/EBPβ
C/EBPα
pre
post
pre
post
RT-PCR
pre
post
C/EBP α
C/EBP β
C/EBP δ
FABP4
LPL
GAPDH
C
KDa
Ctrl+
L.A.
T.M.
MW Marker
35
17
20
70
28
43
34
26
17
95
72
55
43
34
26
Pro-Casp3
Cleaved Casp3
Cleaved Casp7
F.L. Lamin A/C
Cleaved Lamin A/C

OPERATING THEATRE

PATHOLOGICAL CLASSIFICATION

SHORT TERM CULTURES

MOUSE TRANSPLANTATION

MOLECULAR INVESTIGATION

FISH, RT-PCR,
DNA sequencing

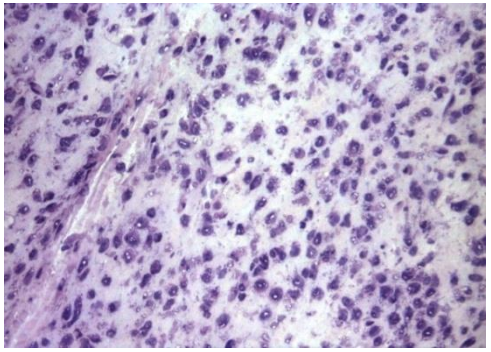
MYXOID LIPOSARCOMA XENOGRAFTS IN MICE MIMICK THE MIXOID LIPOSARCOMA OF THE PATIENTS IN TERMS OF PATHOLOGY, BIOLOGY AND RESPONSE TO TRABECTEDIN

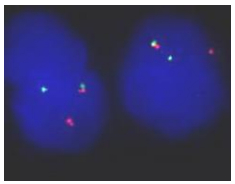
Pre-treatment

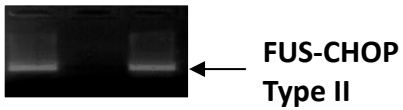
Post-treatment 6 doses of ET

A.

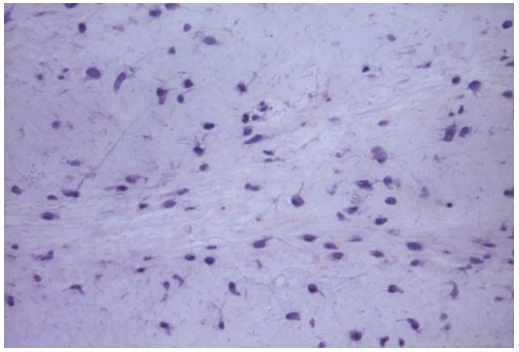
Xenograft (4° P ML017)

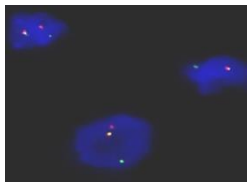


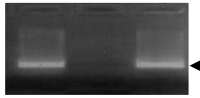




FUS-CHOP Type II



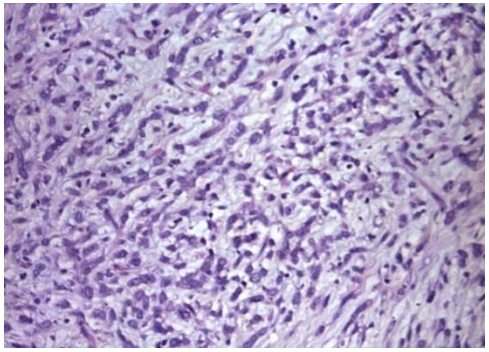


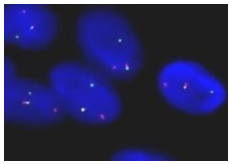


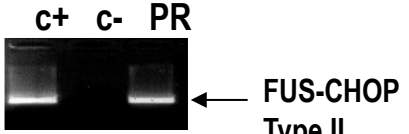
FUS-CHOP Type II

B

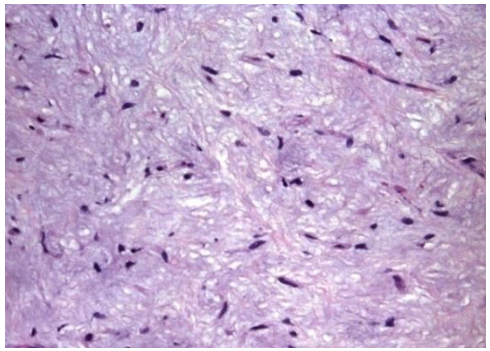
Human Surgical Specimen

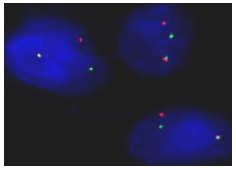


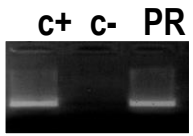




FUS-CHOP Type II



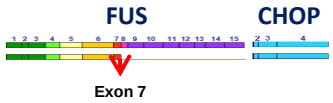




FUS-CHOP Type II

TRABECTEDIN INDUCES ANTITUMOR RESPONSE ASSOCIATED TO ADIPOCYTIC MATURATION AND ANTIANGIOGENIC EFFECTS IN TYPE I/II, BUT NOT IN TYPE III MYXOID LIPOSARCOMA

Type I



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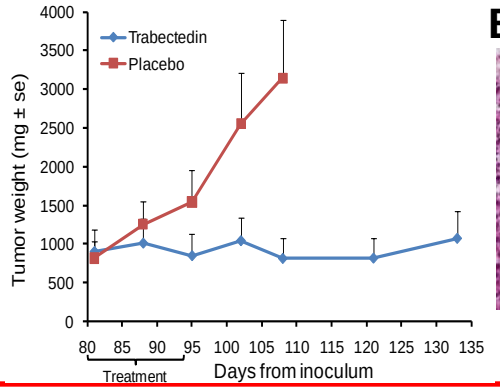

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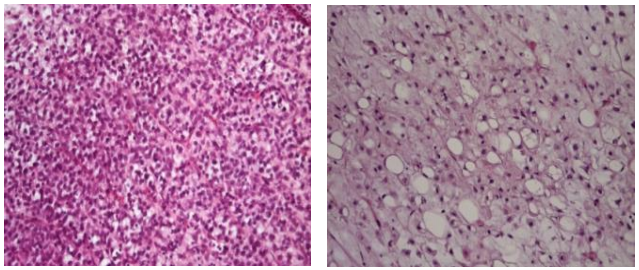

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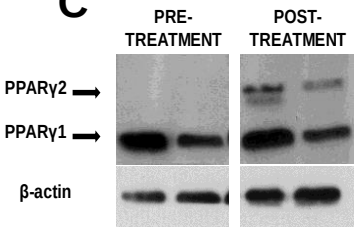
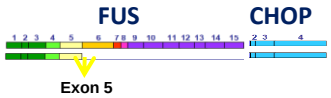
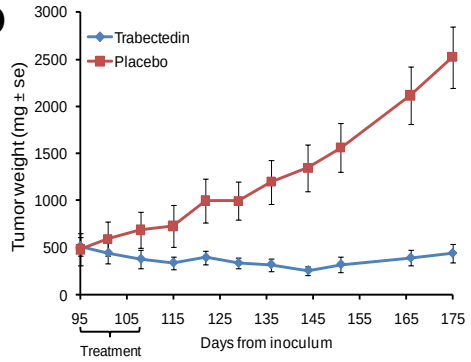


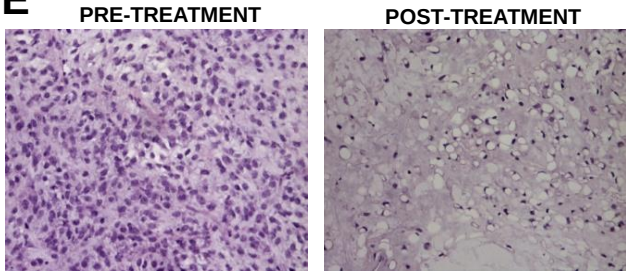
Type II



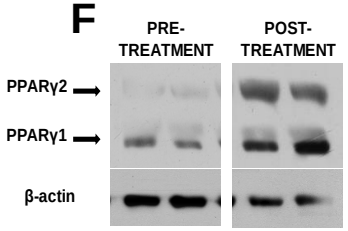
D



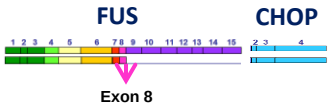
E



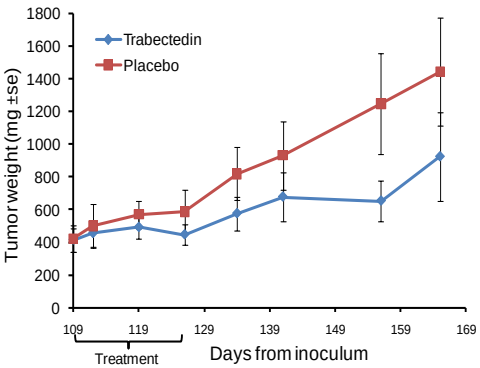
F



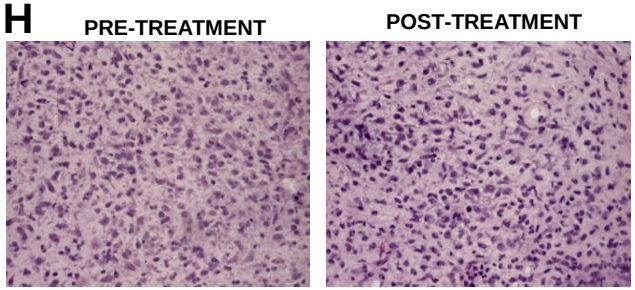
Type III



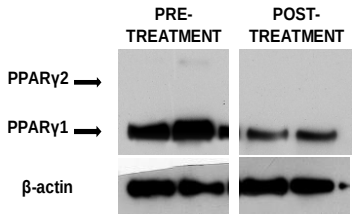
G



H



I



Di Giandomenico et al, Oncogene 2013

TRABECTEDIN DISPLACES FUS-CHOP FROM ITS TARGET PROMOTERS

Type I

Type II

Type III

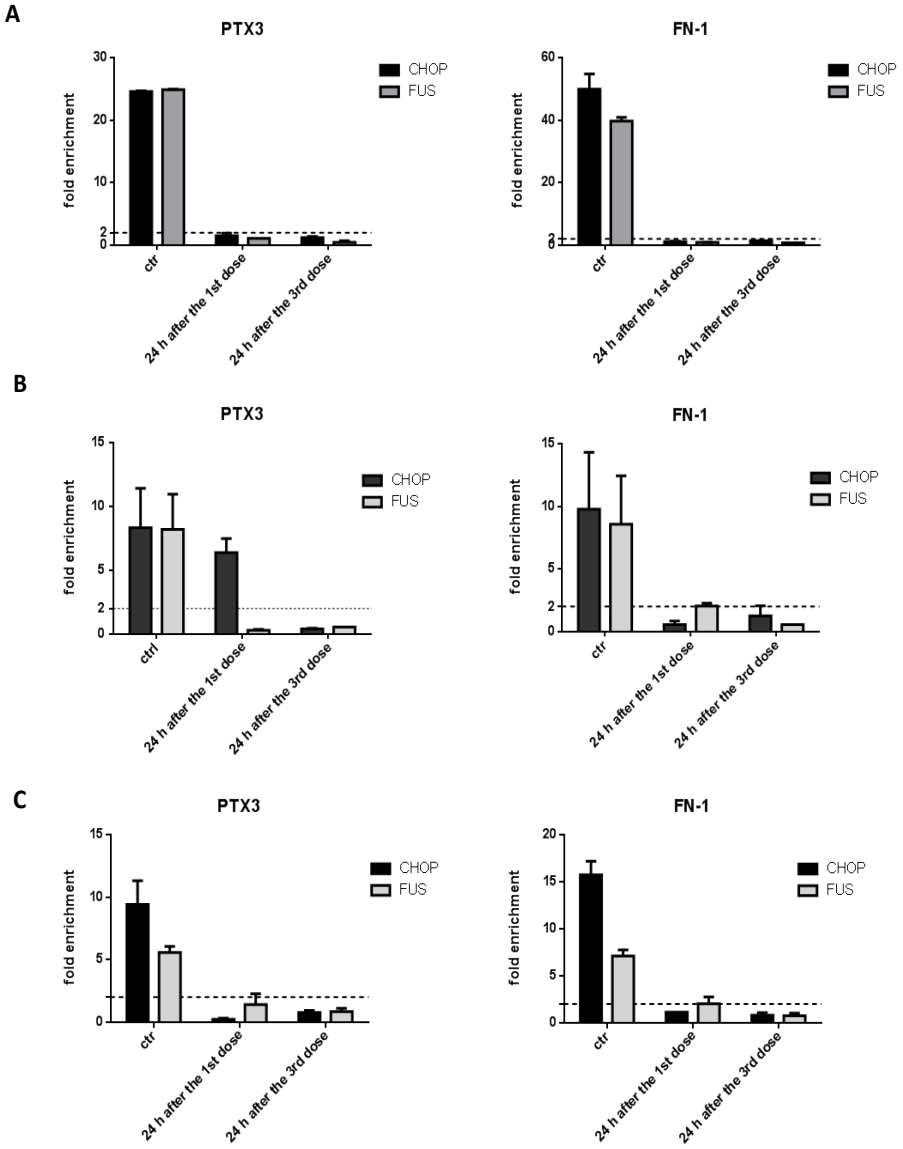


Figure 2: ChIP assay was performed on ML017 (A), ML015 (B) and ML004 (C) xenografts to evaluated the binding of FUS-CHOP to the selected target promoters. Values are reported as fold enrichment over anti-flag antibody. Xenograft mice were treated with trabectedin 0.15 mg/kg every 7 days for 3 times. Samples were collected 24 hours after the first dose, 24 hours after the third dose and 15 days after the end of treatment.

TRABECTEDIN-INDUCED DISPLACEMENT OF FUS-CHOP FROM ITS TARGET PROMOTER LASTS LESS IN TYPE III THAN IN TYPE I/II MLS

Type I

Type II

Type III

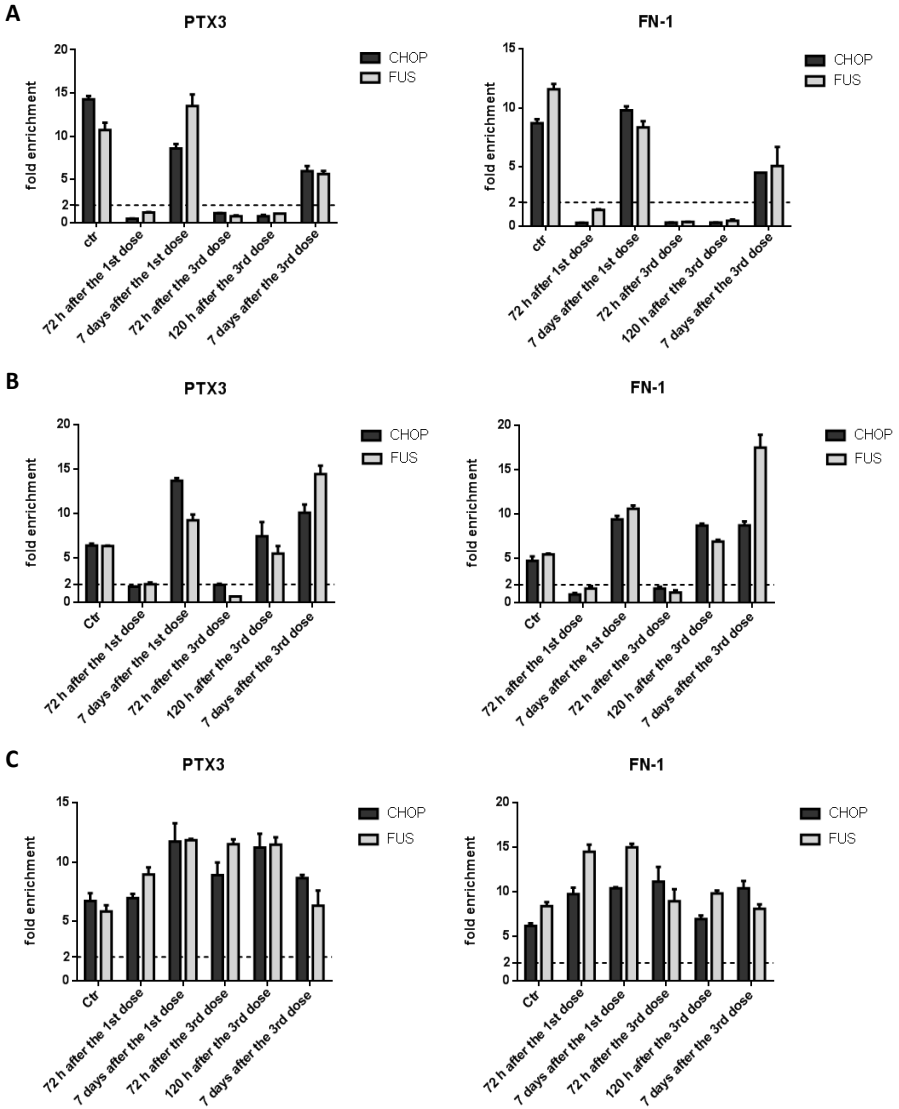


Figure 3: ChIP assay was performed on ML017 (A), ML015 (B) and ML004 (C) xenografts to evaluated the kinetic of rebinding of the three different FUS-CHOP sub-type to PTX3 and FN-1 promoters. Xenograft mice were treated with trabectedin 0.15 mg/kg every 7 days for 3 times. Tumor samples were collected 72 hours after the first dose, 7 days after the first dose, 72 hours after the third dose, 120 hours after the third dose and 7 days after the end of treatment. Values are reported as fold enrichment over anti-flag antibody.

DOXORUBICIN DOES NOT DISPLACE FUS-CHOP FROM ITS TARGET PROMOTERS

Type I

Type II

Type III

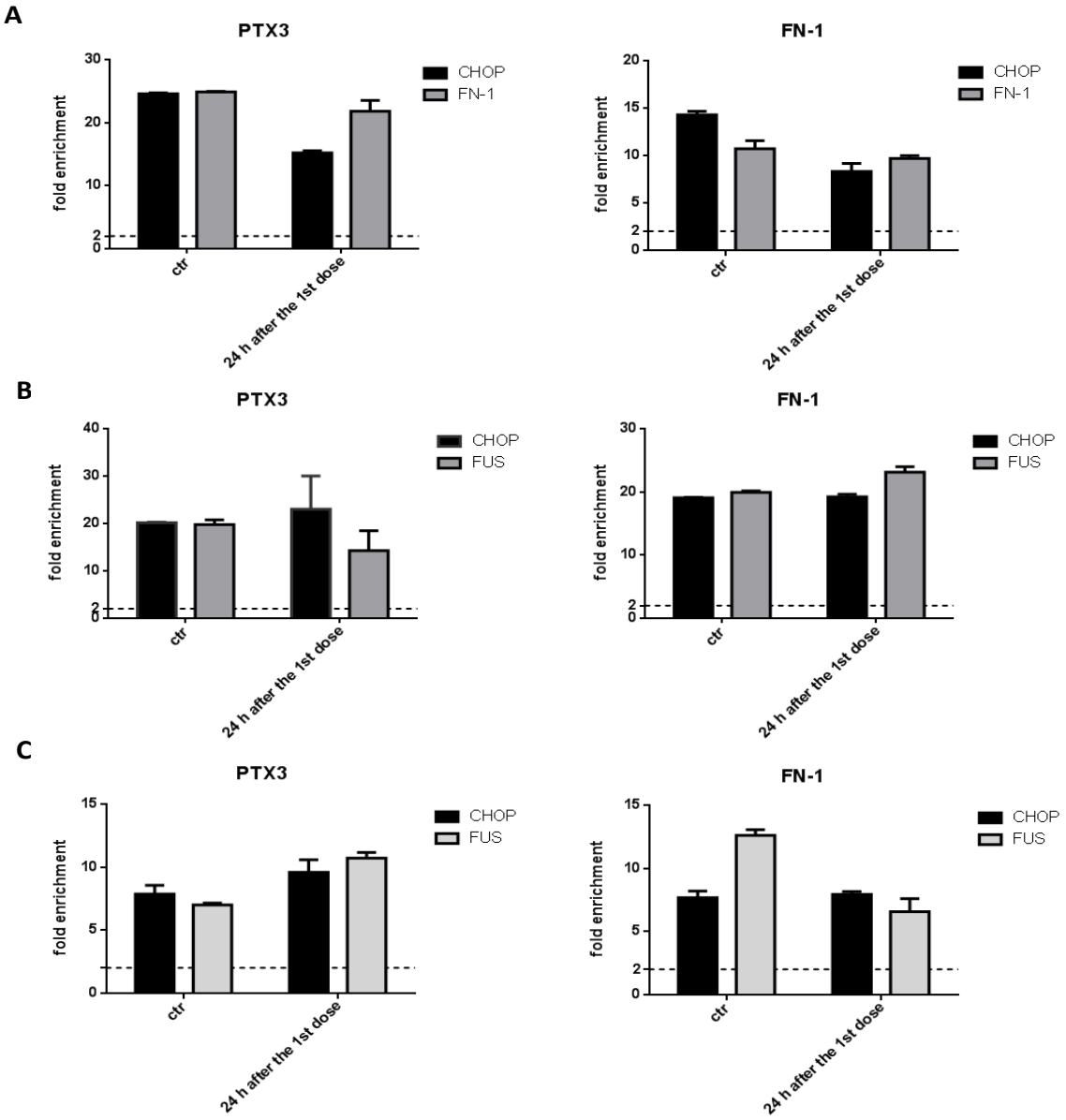
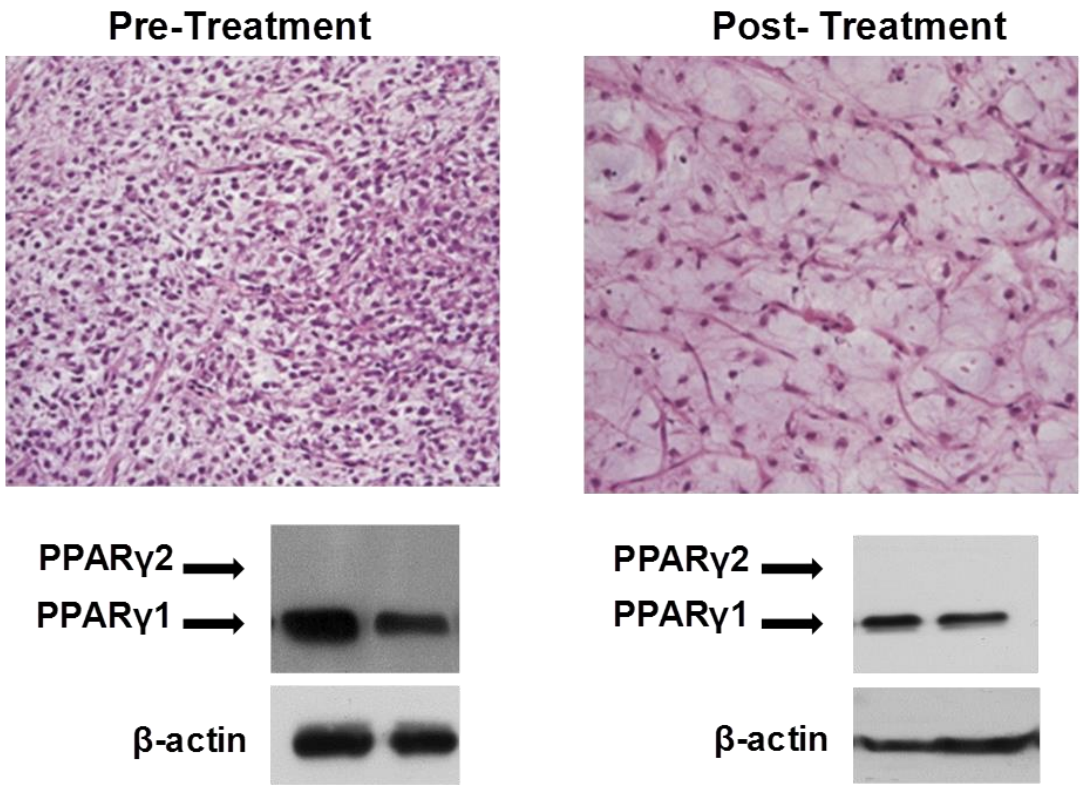
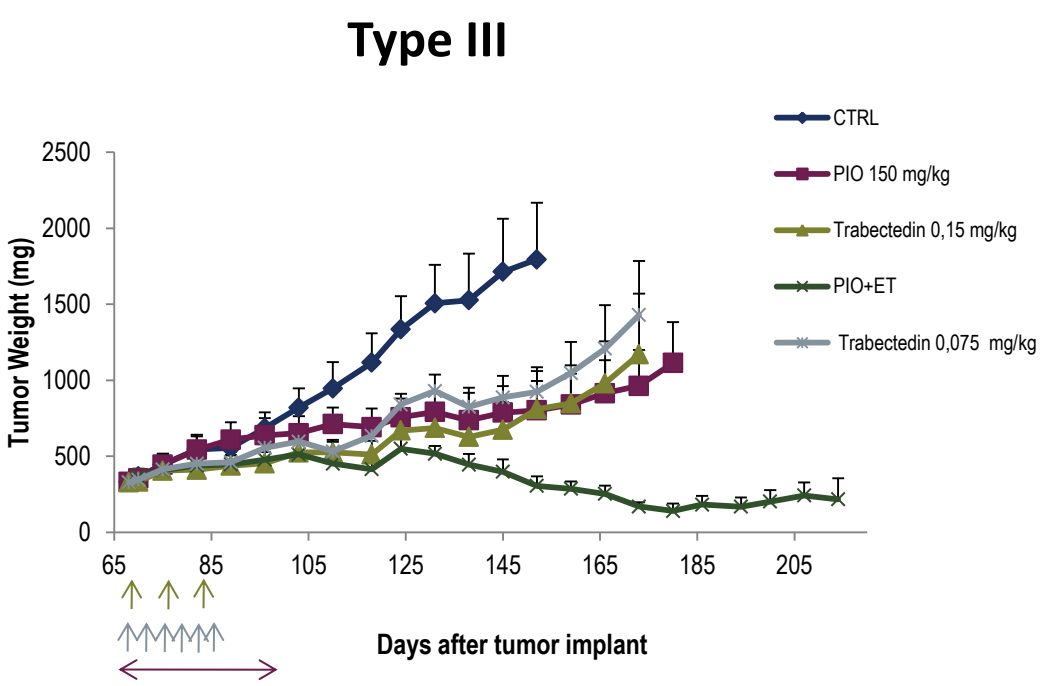


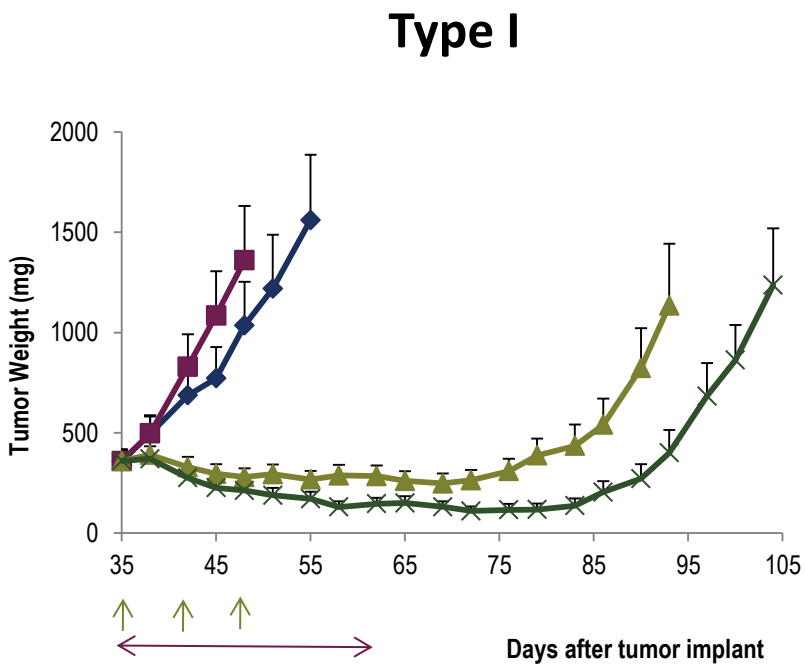
Figure 4: ML017 (A), ML015 (B) and ML004 (C) xenografts were treated with doxorubicin 8 mg/kg and tumors were collected 24 hours after the first dose. The promoters region of PTX3 and FN-1 were amplified. Values were measured as fold enrichment over a Flag control antibody in quantitative RT-PCR analysis.

DOXORUBICIN IS VERY EFFECTIVE, BUT PPARγ2 (MARKER OF ADIPOCYTIC DIFFERENTIATION) IS NOT INDUCED AND THE VASCULAR EFFECT IS NOT AS EVIDENT AS THAT OF TRABECTEDIN

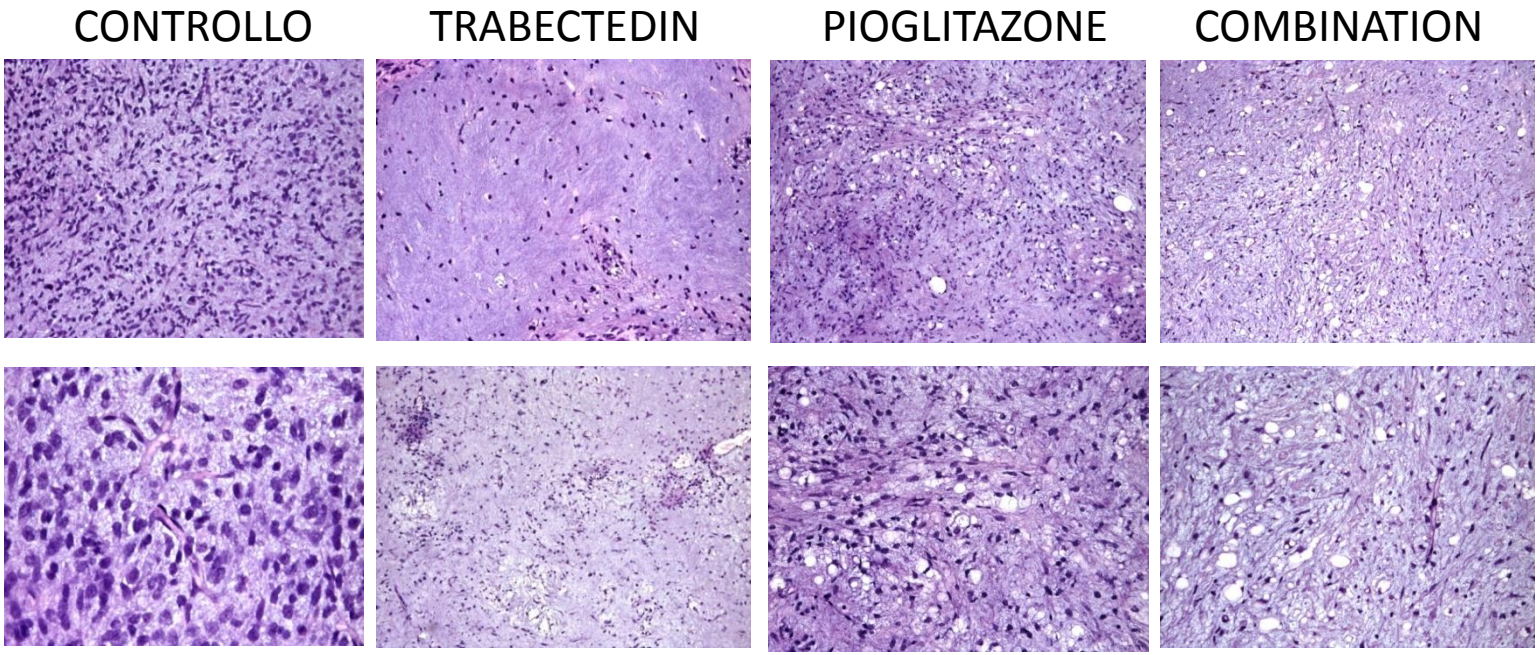


COMBINATION OF PIOGLITAZONE (PPARγ AGONIST) AND TRABECTEDIN ON TYPE III AND TYPE I MYXOID LIPOSARCOMA





H&E STAINING OF TYPE III MYXOID LIPOSARCOMA AFTER TREATMENTS



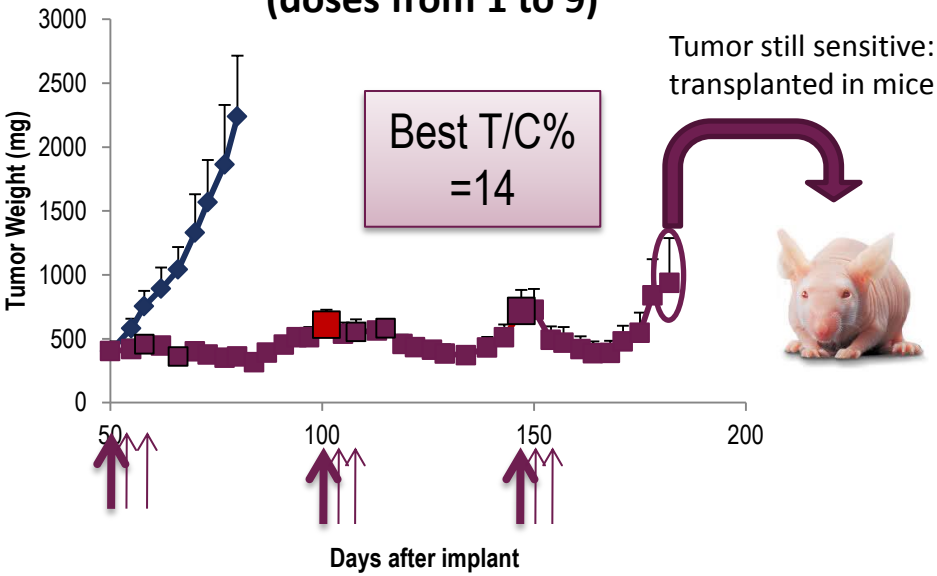
Pioglitazone induces adipocytic maturation and potentiates trabectedin antitumor activity in type III myxoid liposarcoma

ML017 MYXOID LIPOSARCOMA: INDUCTION OF RESISTANCE TO TRABECTEDIN

Vehicle

Trabectedin 0.15 mg/kg q7dx3 iv

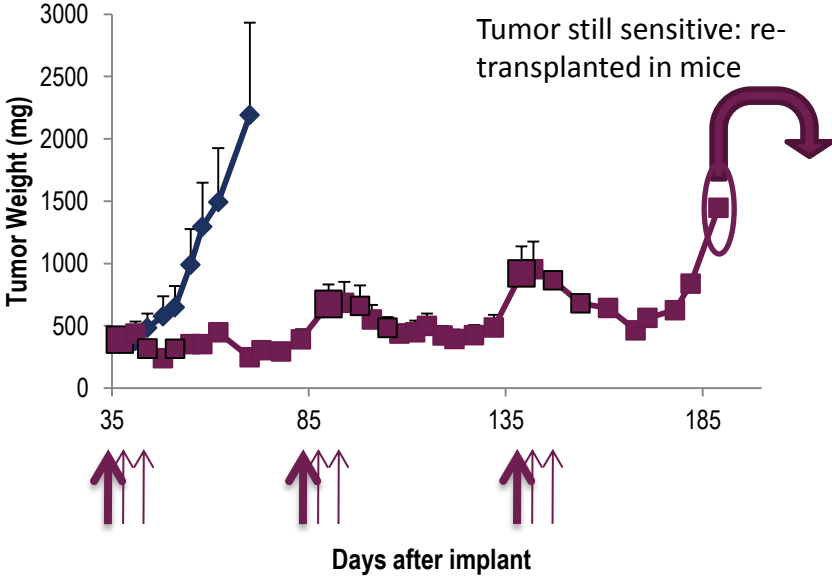
Cycle 1-2-3 (doses from 1 to 9)



Best T/C% =14

Tumor still sensitive: re-transplanted in mice

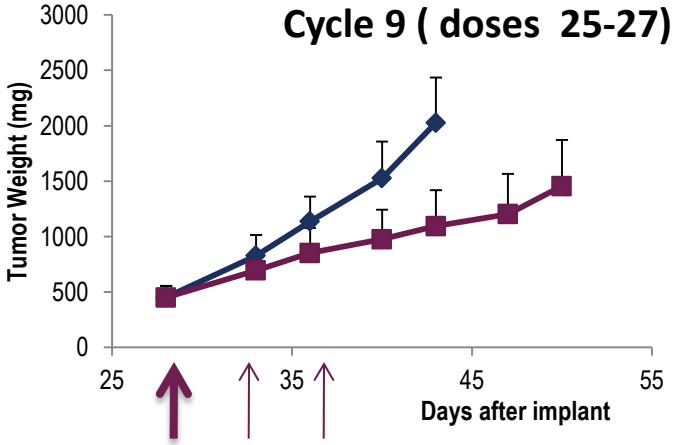
Cycle 4 -5-6 (doses from 10 to 18)



Tumor still sensitive: re-transplanted in mice

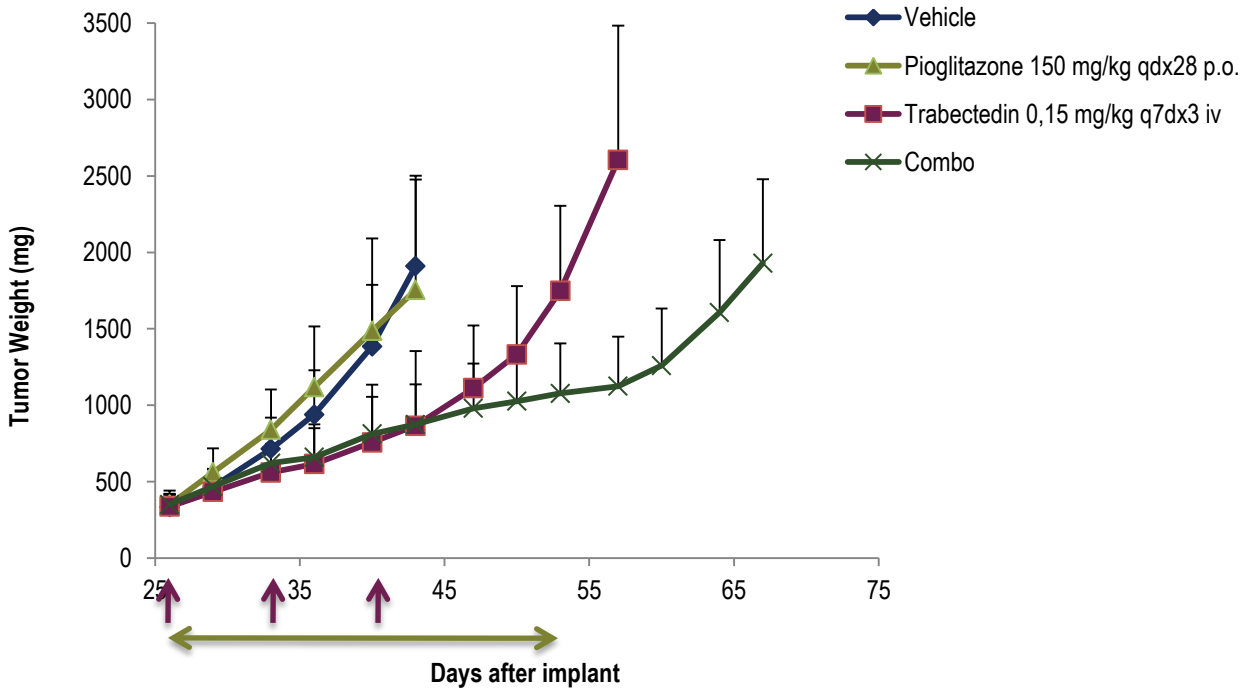
Cycle 7-8

Cycle 9 (doses 25-27)



Best T/C% =54

COMBINATION TRABECTEDIN - PPARγ AGONIST



CONCLUSIONS

Trabectedin is an effective drug in myxoid liposarcoma acting by inhibiting the oncogenic chimeric protein responsible for the disease, thus reactivating adipocytic differentiation.
Most data have been obtained in patients-derived xenografts- that mimic the pathologic molecular features and the drug sensitivity of the human disease.
Nevertheless the effects of the drug appear to be reproduced in the clinic.

PPAR-γ agonists can induce adipocytic differentiation of myxoid liposarcomas, but given alone are moderately effective. In combination with trabectedin they can potentiate its effects, particularly in those tumors that are partially resistant to the drug.

The data provide a rational for clinical investigations on the combination of trabectedin with PPARγ agonists.