ÁREA: CÁNCER

ACTIVE COMBINATIONS FOR THE TREATMENT OF SARCOMA PATIENTS:

OUR EXPERIENCE IN DESIGNING INVESTIGATOR-INITIATED STUDIES

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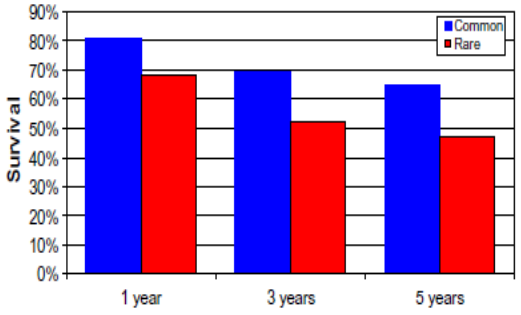
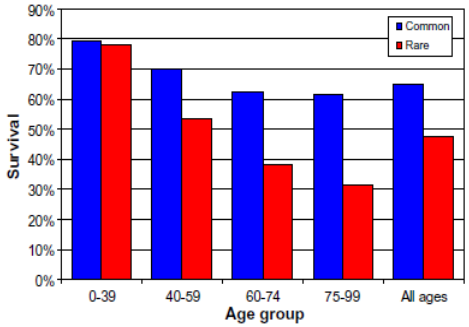
Terapias avanzadas y biomarcadores en sarcomas (ATBSARC)
Grupo Oncología Médica

VI REUNIÓN ANUAL DEL ÁREA DE CÁNCER DEL IIS-FJD
19 de junio del 2024

THE CHALLANGE OF RARE TUMORS

- Difficulties or delay in diagnostic procedure
- Limited Access to centers with clinical expertise in Rare Cancer
- Inadequate funding for clinical research programmes
- Few interest of Pharma Companies in clinical research programmes





LOWER SURVIVAL

Lancet Oncol. 2016 Feb;17(2):136-138
Eur J Cancer 2011 Nov;47(17):2493-511

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THE CHALLANGE OF SARCOMA RESEARCH

- Sarcoma represent 1-2% of solid neoplasms in the adult
- This group encompases more than 70 different histologic subtypes

- Inadequate funding for clinical research programmes
- Few interest of Pharma Companies in clinical research programmes

- LESS APPROVED DRUGS
- LESS THERAPEUTIC OPPORTUNITIES

ACADEMIC RESEARCH

WHAT DO WE DO IN ATBSARC?

- Focus in sarcoma research (preclinical and clinical)

- Developement of academic clinical studies
  - Based on our preclinical results
  - Based on our clinical observations→ preclinical exploration

  - BED ⟷ BENCHSIDE

  - BENSIDE ⟷ BED

ACADEMIC RESEACH DOES NOT MEAN LOW QUALITY RESEARCH

- Multicentric (international) studies
- Central pathological review
- Central radiological review
- Associated translational studies

Abstracts in international congresses
International collaborations
High IF publications

ACADEMIC RESEACH IN SARCOMA IS KEY

10/25 (40%) clinical trials activated in sarcoma unit since 2021 are academic

From those, 7/10 have been designed and are coordinated by our team

A COUPLE OF EXAMPLES:

- Trabectedin + RT
- Immunotherapy in sarcomas: IMMUNOSARC

A COUPLE OF EXAMPLES:

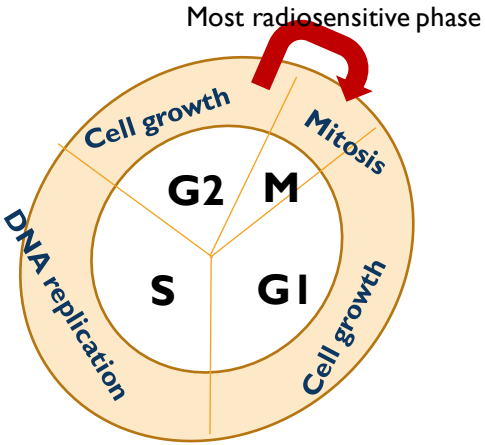
- **Trabectedin + RT**
- Immunotherapy in sarcomas: IMMUNOSARC

TRABECTEDIN + RADIOTHERAPY

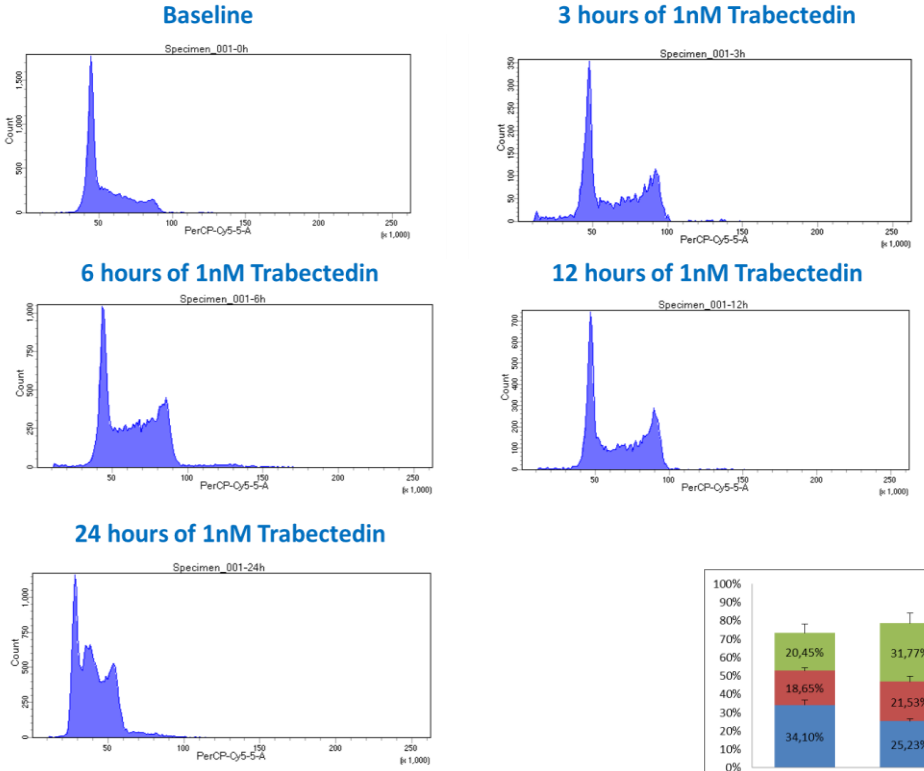
Achieving objective responses in second and further lines in STS is an unmed need (ORR < 10%)

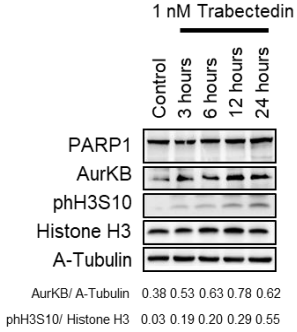
The addition of systemic therapy to RT could enhance the efficacy of RT alone

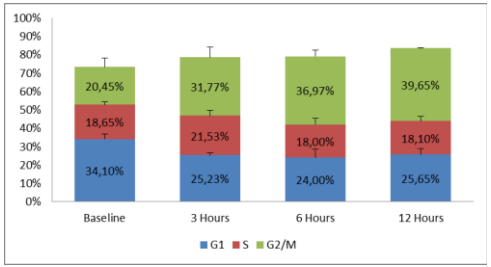
- More responses (radiologic, pathologic)
- More disease control



Trabectedin increases the G2/M fraction

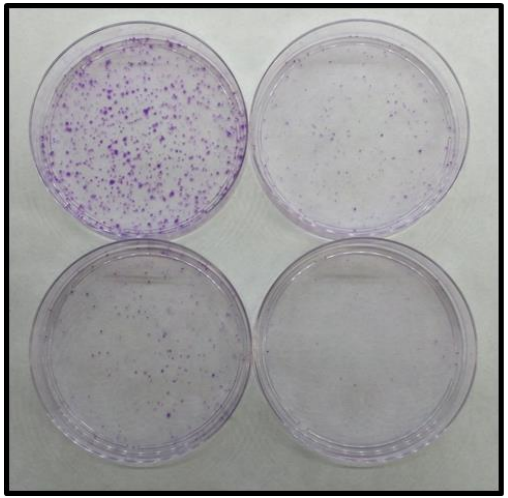


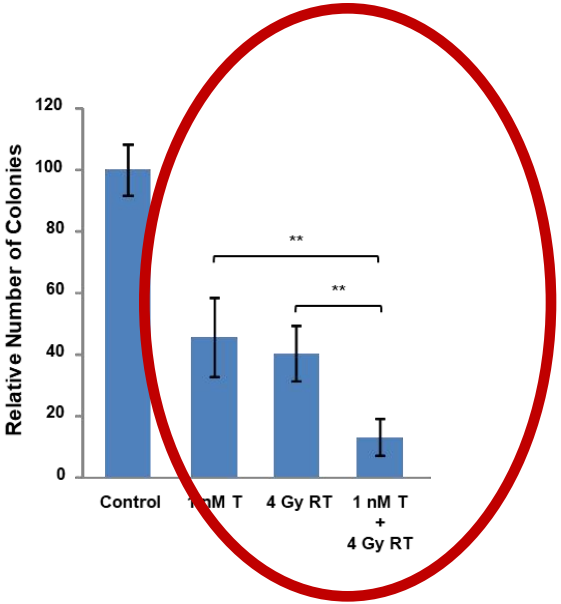




Martin-Broto J, et al. JAMA Oncol. 2020;6:535-541.

- Trabectedin plus radiotherapy is active in sarcoma cell line
- AA leiomyosarcoma



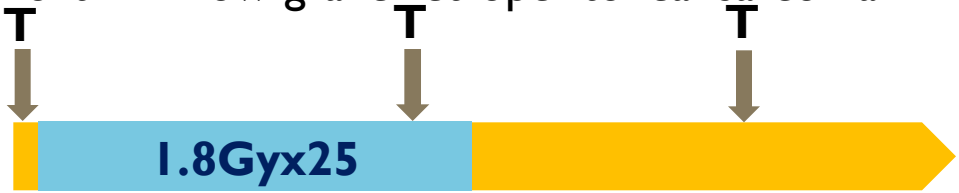


Martin-Broto J, et al. JAMA Oncol. 2020;6:535-541.

TRASTS STUDY (international phase I/II study)

Neoadjuvant Trabectedin + RT (45Gy)

Cohort B→ Localized/locally advanced resectable myxoid liposarcoma
Cohort C→ high-grade retroperitoneal sarcoma
Cohort D→ low-grade retroperitoneal sarcoma



RP2D Trabectedin 1.5 mg/m2

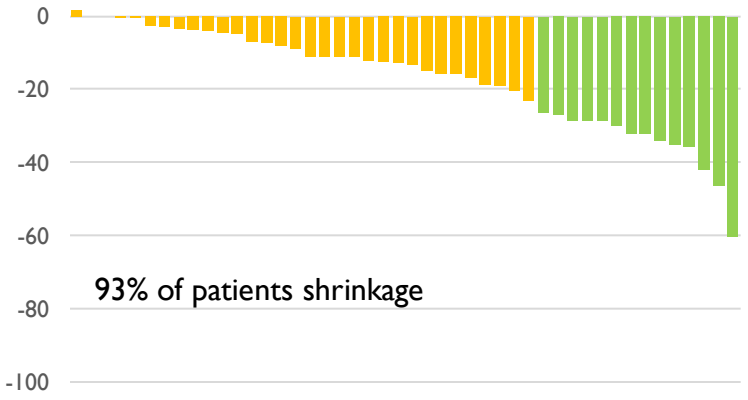
ClinicalTrials.gov Identifier:NCT02275286

JAMA Oncology | Original Investigation

Effectiveness and Safety of Trabectedin and Radiotherapy for Patients With Myxoid Liposarcoma

A Nonrandomized Clinical Trial

Roberta Sanfilippo, MD; Nadia Hindi, MD; Josefina Cruz Jurado, MD; Jean-Yves Blay, MD; Antonio Lopez-Pousa, MD; Antoine Italiano, MD; Rosa Alvarez, MD; Antonio Gutierrez, MD; Inmaculada Rincón-Perez, MD; Claudia Sangalli, MD; Jose Luis Pérez Aguiar, MD; Jesús Romero, MD; Carlo Morosi, MD; Marie-Pierre Sunyach, MD; Chiara Fabbroni, MD; Cleofe Romagosa, MD; Dominique Ranchere-Vince, MD; Angelo P. Dei Tos, MD; Paolo G. Casali, MD; Javier Martin-Broto, MD; Alessandro Gronchi, MD



JAMA Oncol. 2023 May 1;9(5):656-663

Cohort B, published

14% complete path responses

53% path response (> 90%)

Cohort C and D currently ongoing

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JAMA Oncology | Original Investigation

Assessment of Safety and Efficacy of Combined Trabectedin and Low-Dose Radiotherapy for Patients With Metastatic Soft-Tissue Sarcomas

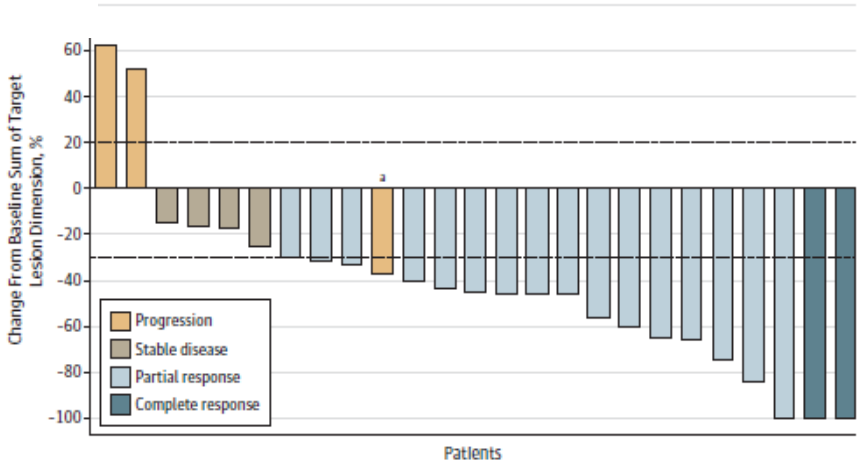
A Nonrandomized Phase 1/2 Clinical Trial

Javier Martin-Broto, MD, PhD; Nadia Hindi, MD; Antonio Lopez-Pousa, MD; Javier Peinado-Serrano, MD; Rosa Alvarez, MD; Ana Alvarez-Gonzalez, MD; Antoine Italiano, MD; Paul Sargos, MD; Josefina Cruz-Jurado, MD; Josep Isern-Verdum, MD; Maria Carmen Dolado, MD; Inmaculada Rincon-Pérez, MD; Paloma Sanchez-Bustos, MSc; Antonio Gutierrez, MD, PhD; Cleofe Romagosa, MD, PhD; Carlo Morosi, MD; Giovanni Grignani, MD; Marco Gatti, MD; Pablo Luna, MD; Ignacio Alastuey, MD; Andres Redondo, MD, PhD; Belen Belinchon, MD; Jordi Martinez-Serra, PhD; Marie-Pierre Sunyach, MD; Jean-Michel Coindre, MD, PhD; Angelo P. Dei Tos, MD, PhD; Jesus Romero, MD, PhD; Alessandro Gronchi, MD; Jean-Yves Blay, MD, PhD; David S. Moura, PhD

Cohort A: Metastatic STS patients

ORR (central): 60%

mPFS 9.9 months
12-months PFSR: 44%
mOS not reached
18-m OS 86%



Martin- Broto J at al. JAMA Oncol. 2020 Apr 1;6(4):535-541.

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ESMO GUIDELINES 2021

SPECIAL ARTICLE

Soft tissue and visceral sarcomas: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

- Trabectedin is an option in advanced STS in second and further lines of treatment. It has proved effective in LMS and liposarcoma[49] [I, B; ESMO-MCBS v1.1 score: 2]. A high antitumour activity has been reported especially in MLS, with a peculiar pattern of tumour response. Clinical benefit with trabectedin is also described in other histological types. In selected cases trabectedin can also be combined with RT, as evidence of safety and activity across different sarcoma types was provided [III, B].[50]

A COUPLE OF EXAMPLES:

- Trabectedin + RT
- **Immunotherapy in sarcomas: IMMUNOSARC**

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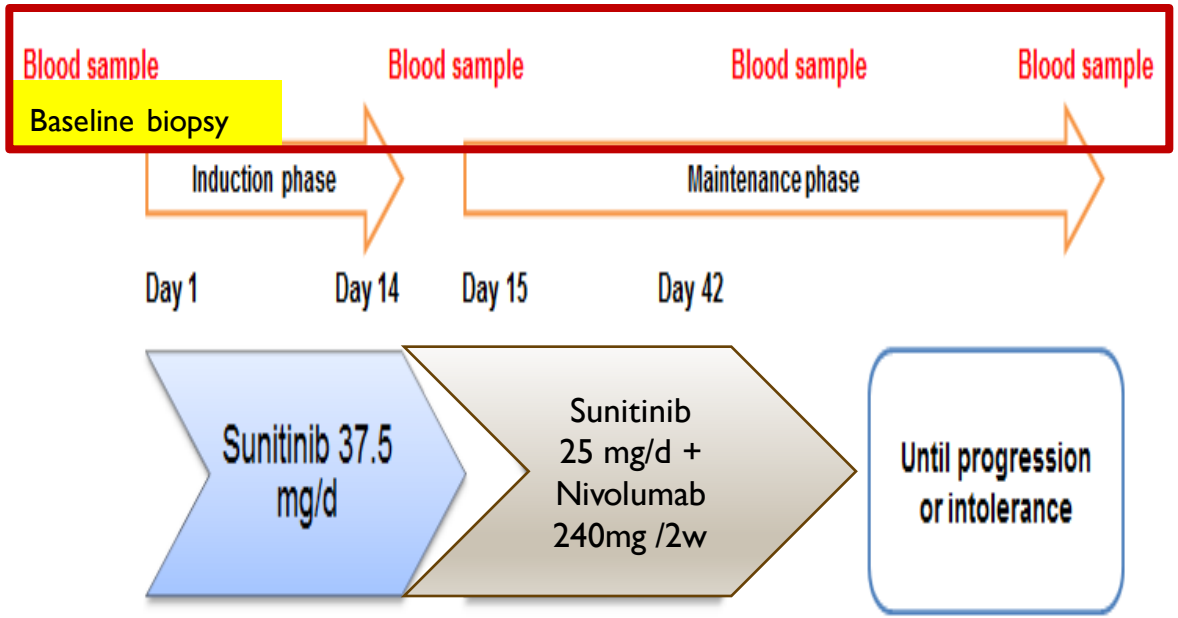
Immunotherapy in sarcomas: IMMUNOSARC

Phase I/II study testing immunotherapy in selected sarcoma subtypes: one of the first studies!!



PRIMARY END-POINT:

- Progression-free survival rate (PFSR) at 6 months (RECIST)
- H0:5%, H1: 15%, α error: 0.05, ß: 0.1.

SECONDARY END-POINTS:

- Overall survival (OS)
- Objective response rate (ORR) by RECIST and CHOI
- Toxicity
- Translational research

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Open access Original research

Journal for ImmunoTherapy of Cancer

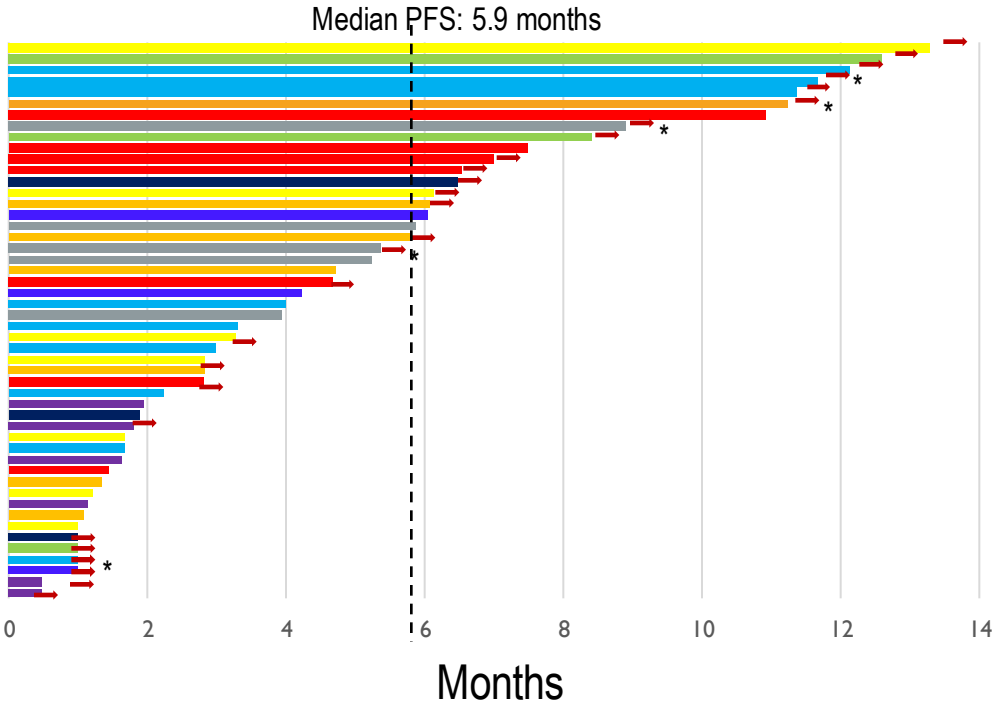
Nivolumab and sunitinib combination in advanced soft tissue sarcomas: a multicenter, single-arm, phase Ib/II trial

Javier Martin-Broto [1,2] Nadia Hindi,[1,2] Giovanni Grignani [3] Javier Martinez-Trufero,[4] Andres Redondo,[5] Claudia Valverde,[6] Silvia Stacchiotti,[7] Antonio Lopez-Pousa,[8] Lorenzo D'Ambrosio,[3] Antonio Gutierrez,[9] Herminia Perez-Vega,[10] Victor Encinas-Tobajas,[10] Enrique de Alava,[11,12] Paola Collini,[13] Maria Peña-Chilet,[2,14,15] Joaquin Dopazo,[2,14,15,16] Irene Carrasco-Garcia,[1,2] Maria Lopez-Alvarez,[2] David S Moura,[2] Jose A Lopez-Martin[17,18]

Synovial sarcoma
Clear cell sarcoma
UPS
Solitary Fibrous Tumor
ASPS
Angiosarcoma
EMC
Epithelioid sarcoma
Other

* Objective responses

Results from Phase I/II study



IMMUNOSARC II TRIAL

Rationale	IMMUNOSARC I Phase I	IMMUNOSARC I Phase II	IMMUNOSARC II Expansion coh	IMMUNOSARC II New Cohorts

BASQUET TRIAL PART SUNITINIB + NIVOLUMAB

Chondro	EMCh	AngioS	SFT	ASPS	CCS
24	22	23	24	18	23
ASCO 2024 Oral		CTOS 2023 Oral ESMO 2023 poster	ASCO 2023 Poster		ESMO 2024 Oral?

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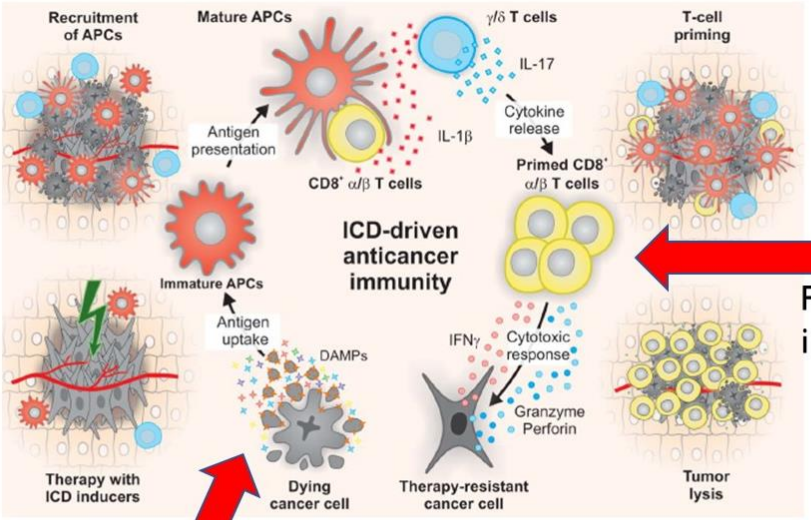

Oncoimmunology. 2014 13;3(9):e955691

PD1/PDL1 inhibitors

IMMUNOGENIC CELL DEATH

- Cohorts 7 and 8
- Addition of nivolumab to first line CHT

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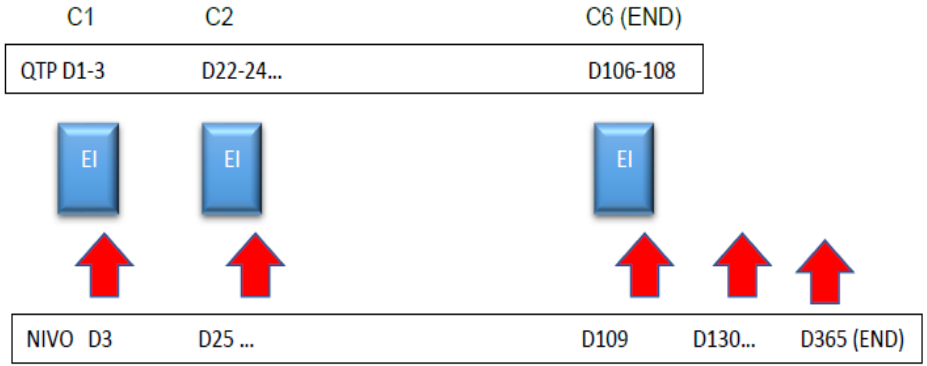
UPS

EPI+IFOS+NIVOLUMAB
PHASE Ib

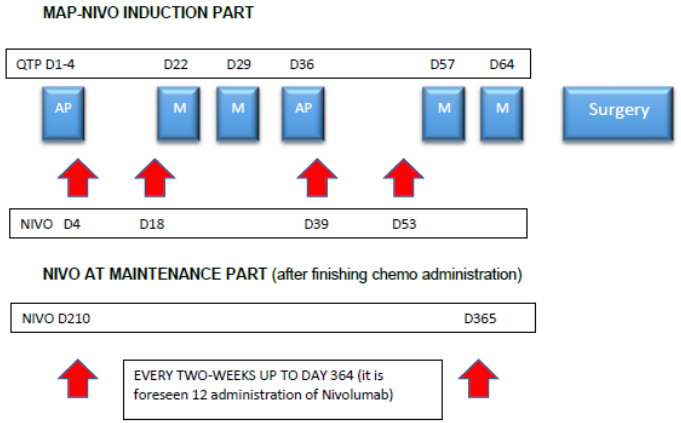


LMS

DOXO+DTIC+NIVO
PHASE Ib

OST (MI)

NIVOLUMAB + MAP in
upfront (Phase I-II)



LEVEL 0: Nivolumab at 360 mg/3w
LEVEL -1: Nivolumab at 240 mg/3w

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.- Median follow-up: 8 months (2-12)

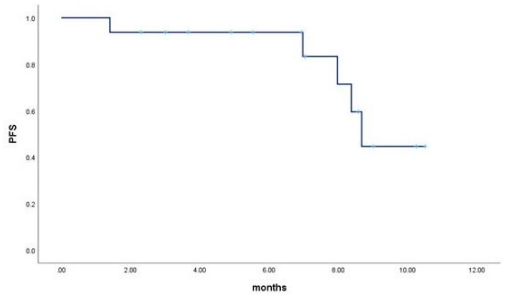
.- #Cycles (combo): 94. Median: 6 (1-6)

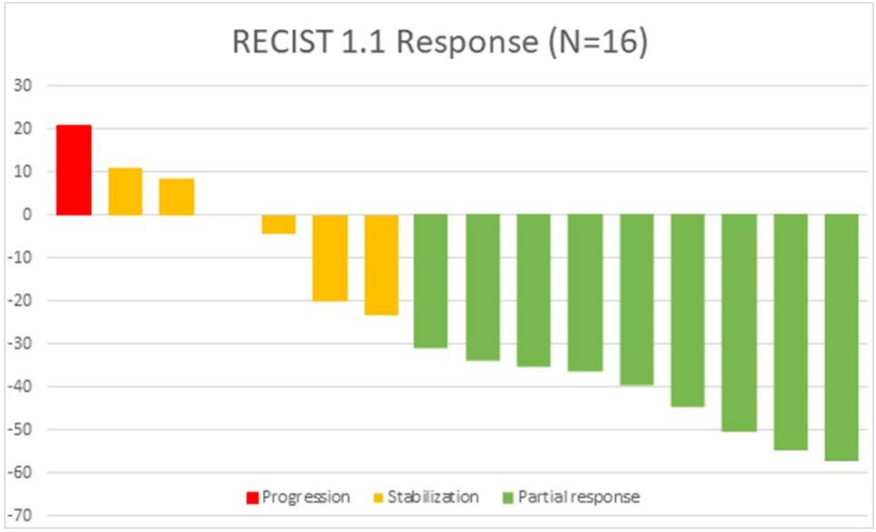
.- ORR from 16 evaluable patients:

9 PR (56.2%); 6 SD (37.5%); 1 PD (6.3%)

.- mPFS 8.67 months (95% CI: 7.96-9.37)

.- Median to response: 1.7 months (95% CI1.1-9)





In press: JCO!!!

2023 ASCO ANNUAL MEETING

#ASCO23

PRESENTED BY: Javier Martin Broto

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

CONCLUSIONS

- Trabectedin plus RT is an active and safe therapeutic option, and our preclinical data support the synergy of the strategy.
- This regimen is currently widely used

- Immunotherapy can be active in selected sarcoma subtypes. IMMUNOSARC has provided clinical data of its activity and preclinical data for the identification of molecular predictive factors

CONCLUSIONS

Our group has experience in the developement of high-Quality academic clinical trials (all the steps: concept, design, pharma negotiation for Budget, coordination, data analysis, traslational studies, publication) → Expertise to share