Sarcoma: Insights in biology and new therapies

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Lille University and Centre Oscar Lambret

15th BSMO – December 2021

Conflicts of interest

- Funding for academic research
  - BAYER Healthcare, Pharmamar, Roche

- Board
  - BAYER Healthcare, Jansen-Cilag, Astellas, MSD, BMS, Ipsen, Astra-Zeneca, ImmunoScore, Pfizer

Sarcoma: Insights in biology and new therapies

- Sarcomas
- Tailored therapies according to histological subtypes
- Histology-agnostic approach
- Immunotherapies

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Four major ideas

- Altogether rare, <6/100000/year
- >150 sub-types/ complex diagnosis (misdiagnosis: 30%)
- Localized stage: cured in 70% of cases – critical role of **R0**
- Advanced stages
  - Cured in less than 5% of cases
  - Median OS: 18-24 months
  - Hard-to-treat diseases – unmet medical needs

Tailored therapies according to subtypes

Histological subtypes	Targets	Doxorubicin	Agents as 2nd-line
Liposarcoma	Multiple	Sensitive +++	Trabectedin, eribulin
Leiomyosarcoma	No	Sensitive +++	Trabectedin, gemcitabine, Pazopanib, DTIC …
Undifferentiated Sarcomas	No	Sensitive +++	Ifosfamide, pazopanib, DTIC
Synovial sarcoma	No	Sensitive +++	Ifosfamide, pazopanib
Angiosarcoma	No	Sensitive	Taxanes, gemcitabine, pazopanib
PEComa	mTOR	Sensitive	mTOR inihibitor, gemcitabine

Tailored therapies according to subtypes

Histological subtypes	Targets	Doxorubicin	Agents as 1st line
GIST	KIT/PDGFR	Resistant	**1st-line:Imatinib** Sunitinib, Regorafenib
Low Grade Endometrial stromal Sarcoma	Estrogen-R	Resitant	**1st-line: Castration and aromatase inhibitor** Progesterone
A/E Rhabdomyosarcoma	No	Sensitive	**1st-line: Vinristine, Actinomycine, Ifosfamide** temozolomide/irinotecan
Solitary Fibrous Tumour	Angio-genesis	Sensitive	**1st-line: TKI inhibitors** gemcitabine, TMZ, DTIC
Alveolar soft part S		Resistant	**1st-line: TKI inhibitors**
Clear cell Sarcoma		Resistant	

Tailored therapies according to subtypes

Histological subtypes	Targets	Doxorubicin	Agents as 1st line
Chordoma	PDGFR	Resistant	**1st-line: Imatinib**
Giant cell bone tumor	RANK	Sensitive	**1st-line: Denosumab**
Inflammatory myofibroblastic tumor	ALK	Sensitve	**1st-line: ALK inhibitor**
Epithelioid hemangioendothelioma	No	Resistant	**1st-line: Active surveillance**
Dermatofibrosarcoma	PDFGR	Resistant	**1st-line: Imatinib**

Tailored therapies according to histological subtypes: What's new ?

- New TKI for GIST
- New treatments for Diffuse-type tenosynovial giant-cell tumors
- Tazemetostat ?
- Trabectedin + doxo in LMS

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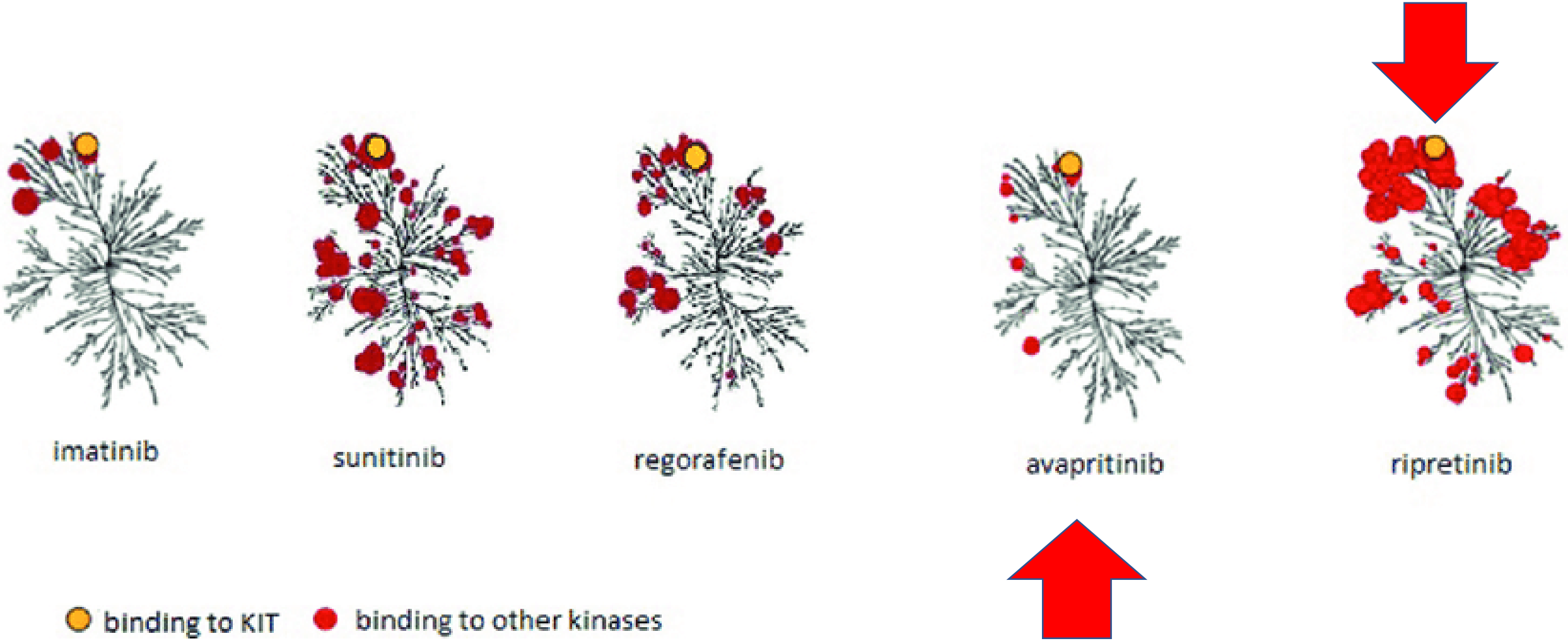
Ripretinib a multikinase inhibitor with very broad spectrum activity

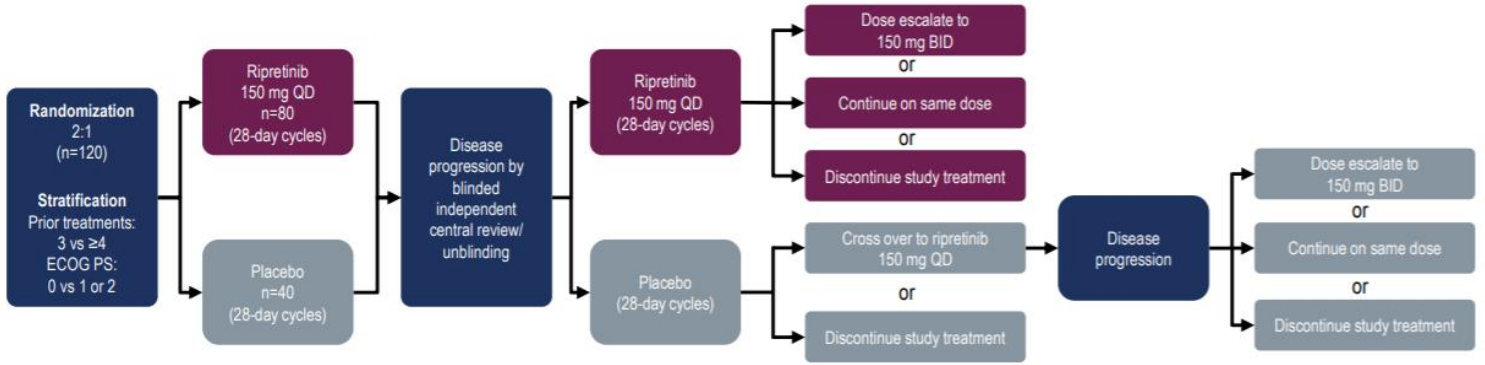


Avapritinib a TKI with highly targeted activity

Phase III INVICTUS ripretinib as 4th line treatment

INVICTUS: Randomized Phase 3 Study Design

Evaluated ripretinib as ≥4th line therapy in patients with advanced GIST



Primary endpoint

PFS

(per modified RECIST based on **B**linded **I**ndependent **C**entral **R**eview [BICR])

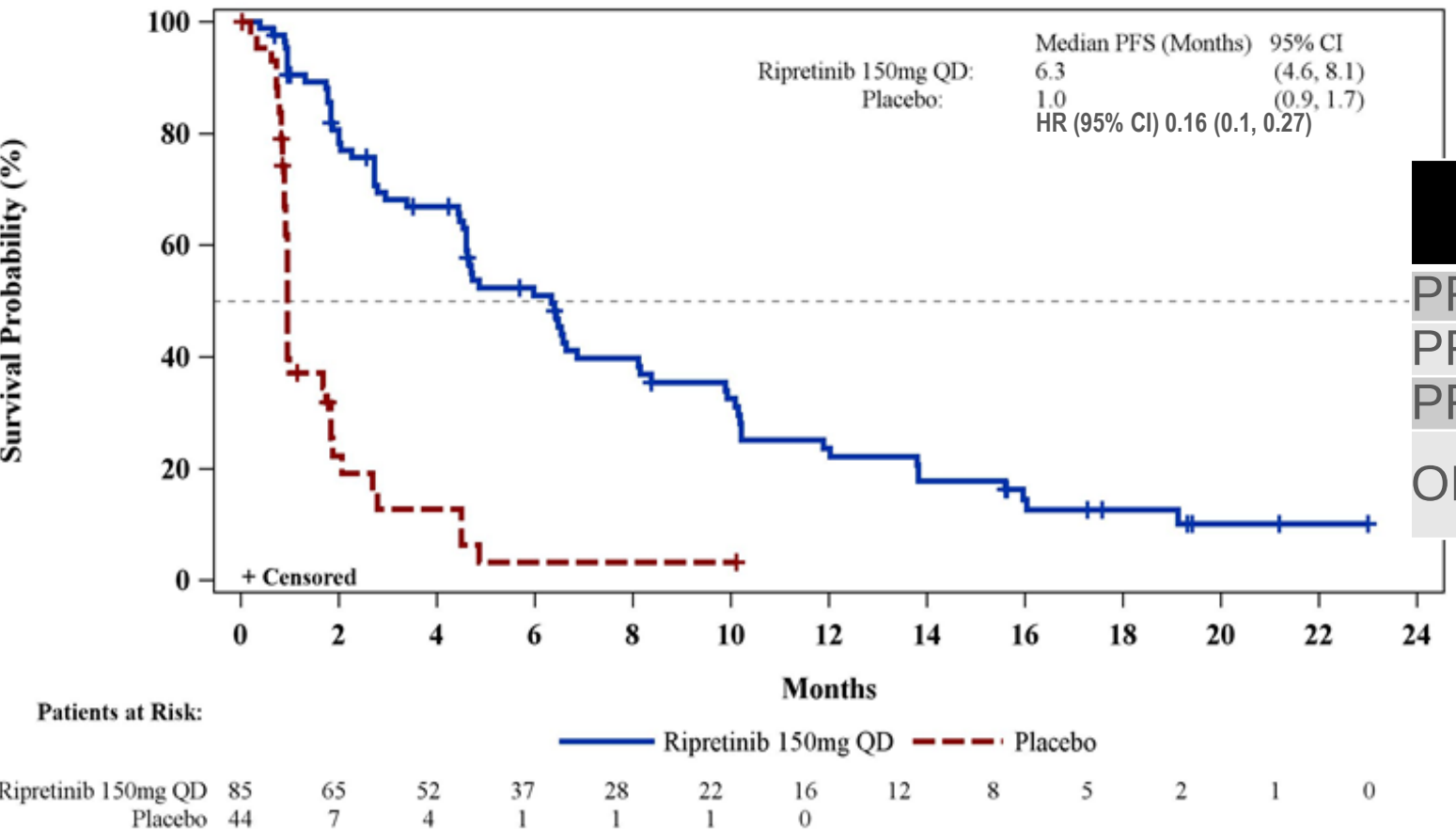
Select Secondary endpoints

- **Objective response rate (ORR)** assessed by BICR (Key endpoint)
- **Overall survival (OS)**

Data cutoff
May 31, 2019

BARCELONA 2019 ESMO congress

Phase III INVICTUS ripretinib as 4th line treatment

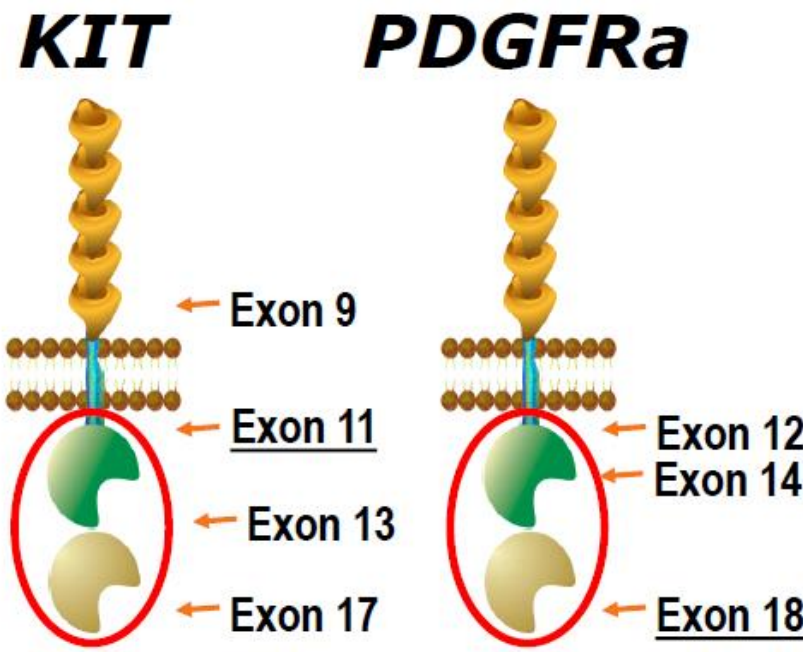


	Ripretinib (n = 85)	Placebo (n = 44)
PFS 6 months, %	51.0%	3.2%
PFS 12 months, %	23.6%	NE
PFS 18 months, %	12.6%	NE
ORR, n (%)	10 (11.8%)	0

Blay et al. Lancet Oncol 2020;21(7):923-934

Avapritinib

TKI targeting imatinib-resistant KIT/PDGFR mutations



		BLU-285 IC_{50}	Imatinib IC_{50}
KIT Exon 11 deletion	JM domain mutations	0.6 nM	12 nM
KIT Exon 11 V560G		1 nM	87 nM
KIT Exon 11/13	ATP binding site mutations	11 nM	9160 nM
KIT Exon 11/14		28 nM	19650 nM
KIT Exon 17	Activation loop mutations	<2 nM	60–12750 nM
KIT Exon 17 D816V		0.27 nM	8150 nM
PDGFRα Exon 18 D842V		0.24 nM	759 nM

Heinrich M, et al. *CTOS 2018*

NAVIGATOR Trial

- Avapritinib (BLU-285), 300 mg/jour

- Phase I/II with 56 pts with D842V-mutated GIST
  - ORR: 91%
  - CBR: 98%
  - PFS: 34 months
  - Cognitive effects: 57%

Jones et al. Eur J Cancer 2021;145:132

TKI in GIST

Name	Type	Initial targets	Indication
Imatinib	II	BCR-ABL1	KIT-positive (CD117) uneresectable or metastatic GIST
Sunitinib	II	FLT3, VEGFR	GIST after intolerance or progression to imatinib
Regorafenib	II	VEGFR	GIST previously treated with imatinib and sunitinib
Repritinib	II	KIT	GIST previously treated with imatinib, sunitinib and regorafenib
Avapritinib	I	KIT, PDGFR	D842V PDGRα GIST

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- Tazemetostat?
- Trabectedin + doxo in LMS

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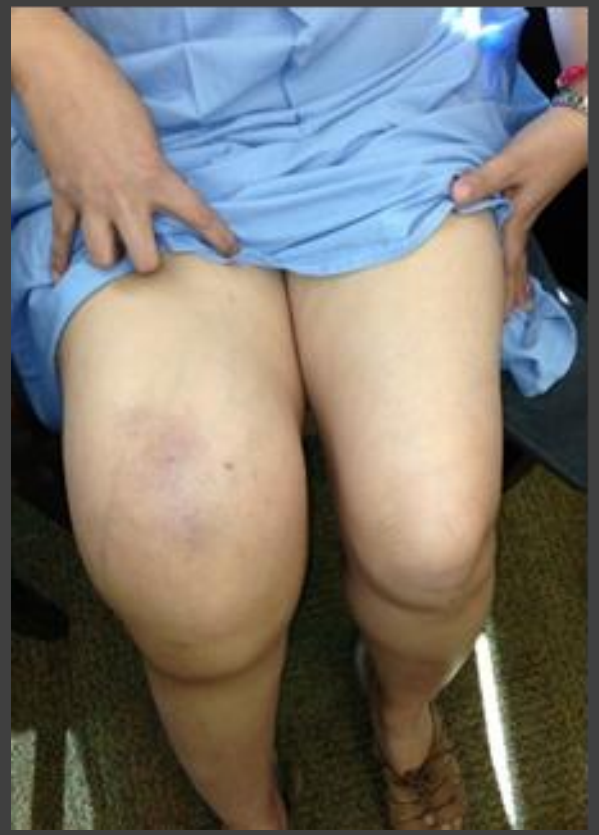
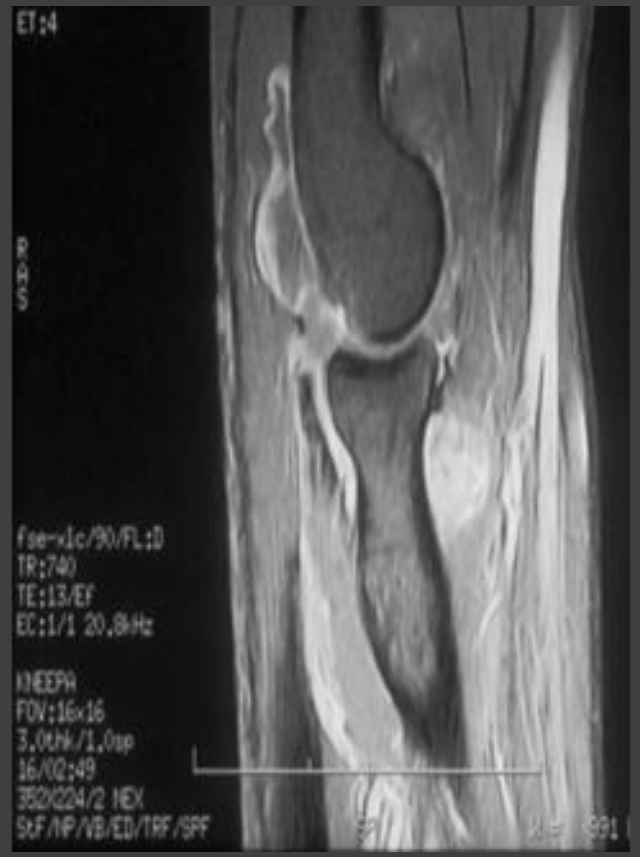
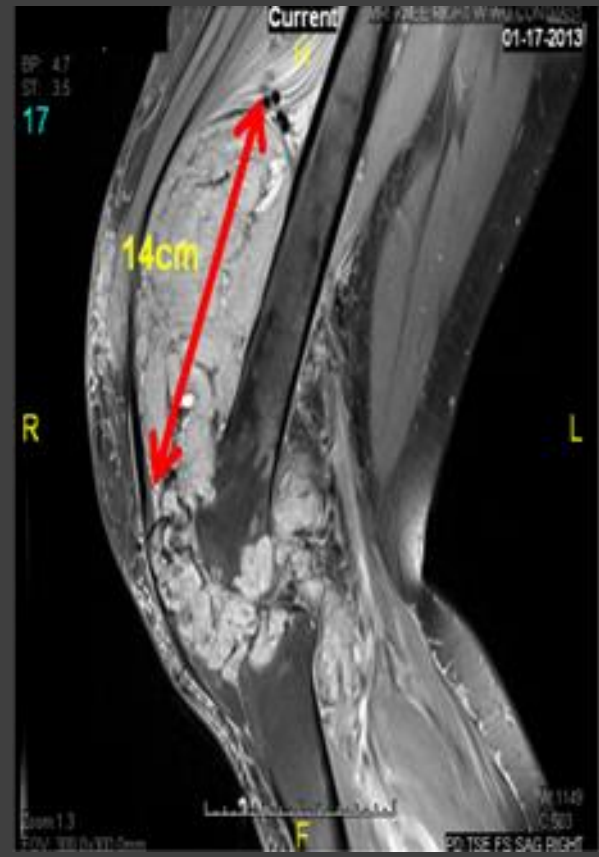
Diffuse-type tenosynovial giant-cell tumors

- col3A6-CSF1 fusions
- Para-articular masses +/- lung metastasis
- Functional impairment







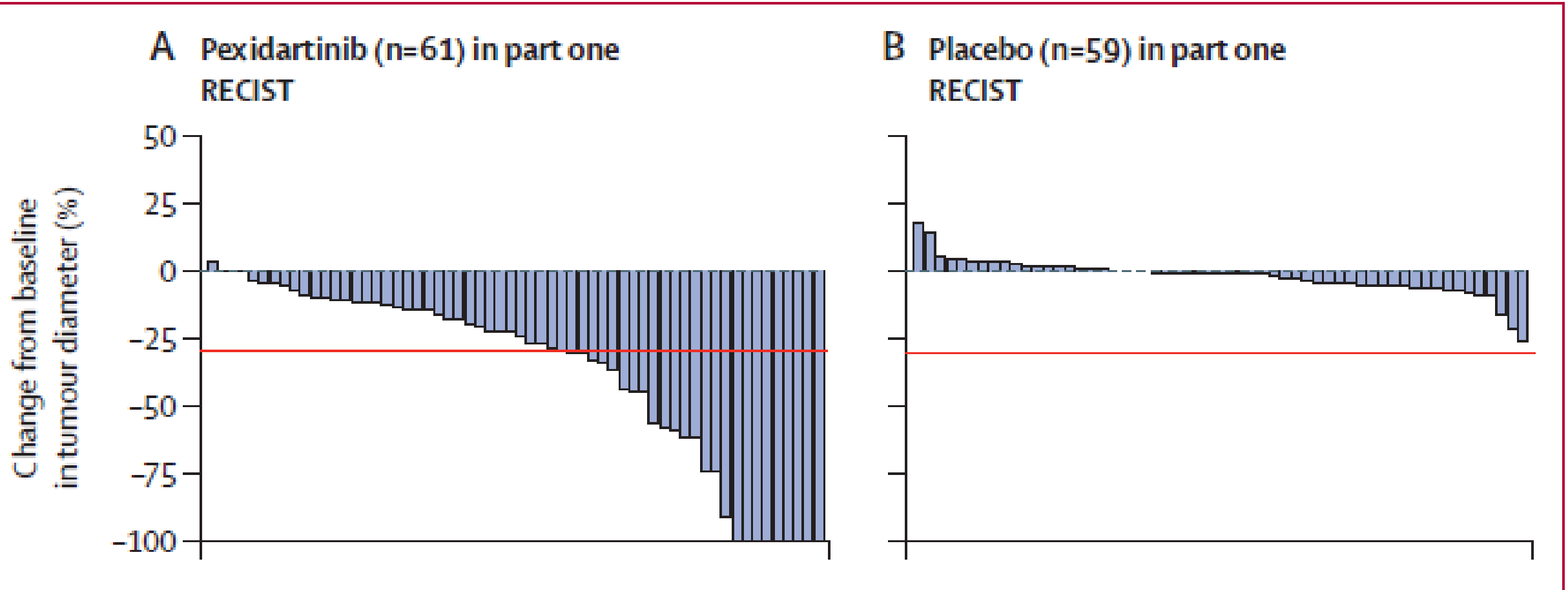
Diffuse-type tenosynovial giant-cell tumors

Drug	Study	Main results
Imatinib	Retrospective (1)	ORR 19% - symptomatic improvement 73%
Nilotinib	Phase II (2)	3-month PFR: 93%
Emactuzumab	Phase I (3)	ORR: 79%
pexidartinib	Phase III (4)	ORR: 60% - Liver toxicity

(1) Cassier et al. Cancer 2012; (2) Gelderbloom et al. Lancet Oncol 2018; (3) Cassier et al. Eur J Cancer 2020; (4) Gelderblom et al. Cancer 2021

Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial

William D Tap, Hans Gelderblom, Emanuela Palmerini, Jayesh Desai, Sebastian Bauer, Jean-Yves Blay, Thierry Alcindor, Kristen Ganjoo, Javier Martín-Broto, Christopher W Ryan, David M Thomas, Charles Peterfy, John H Healey, Michiel van de Sande, Heather L Gelhorn, Dale E Shuster, Qiang Wang, Antoine Yver, Henry H Hsu, Paul S Lin, Sandra Tong-Starksen, Silvia Stacchiotti, Andrew J Wagner*, on behalf of the ENLIVEN investigators†*



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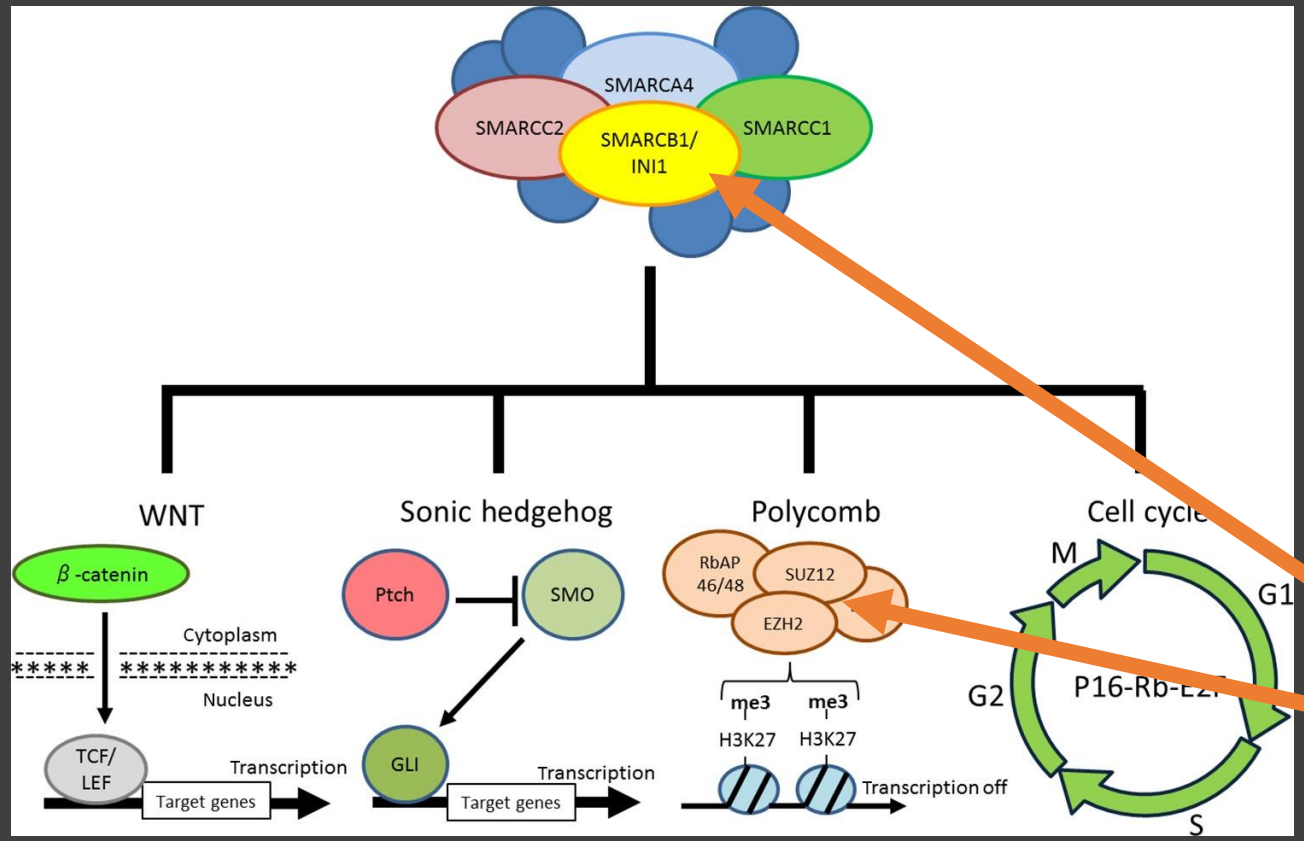
Epithelioid sarcoma



- Rare
- Young patients
- Upper extremities
- 15% multifocal at diagnosis
- 15% M1 at diagnosis
- Lymph nodes, lung, bone and brain met
- Response to doxo: less than 20%

- Lost of INI1
- Deregulation of cell proliferation depending on EZH2

Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1

- Phase II trial
- 800 mg tazemetostat orally twice per day in continuous 28-day cycles
- 62 pts
- ORR: 9 (15%)
- PFS: 5.5 months
- OS: 19 months

Goudner et al. Lancet Oncol 2020(11):1423

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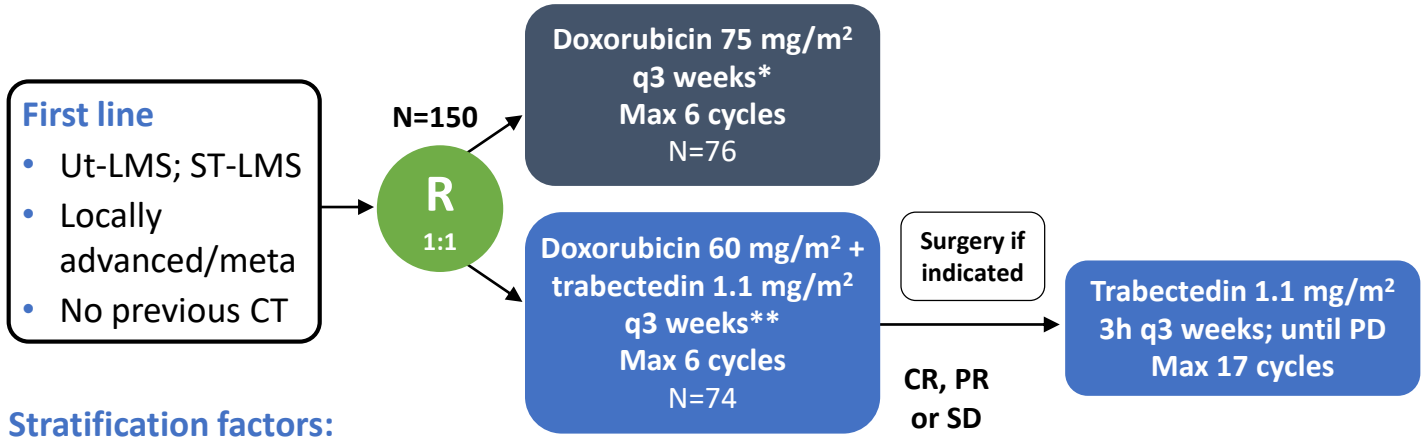
LMS-04: Study design

Background:

LMS-04 (NCT02997358) = Randomised Phase III multicentric study comparing efficacy of doxorubicin with trabectedin followed by trabectedin in non-progressive patients versus doxorubicin alone as first-line therapy in patients with metastatic or unresectable leiomyosarcoma (uterine or soft tissue)

LMS 04: Ph-III first-line therapy for locally advanced/metastatic LMS



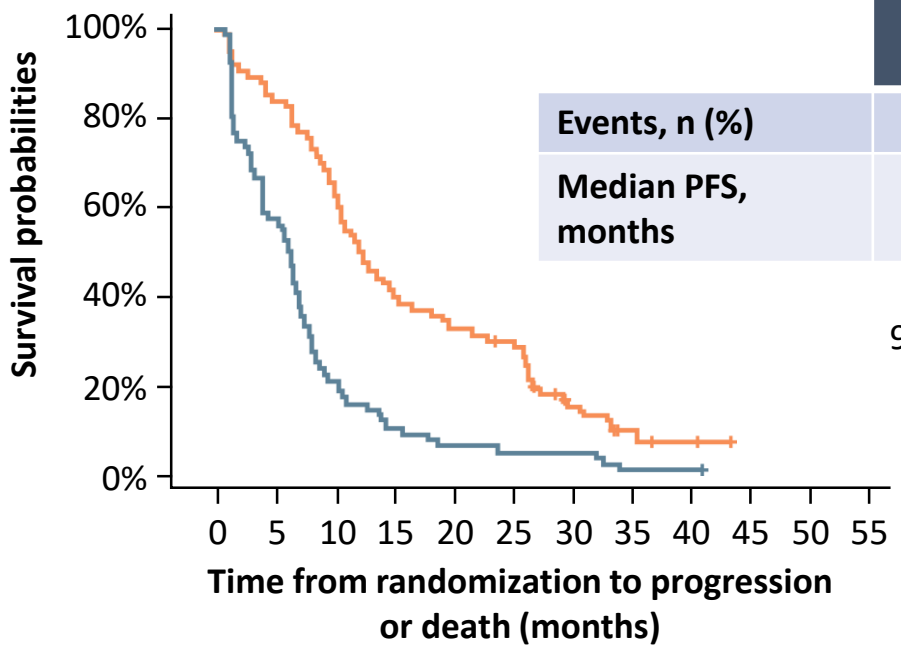
Stratification factors:

- Uterus vs soft tissue
- Locally advanced vs metastatic

* + Lenograstim 150 µg/m²/day s.c. d3-9; ** + Pegfilgrastim 6 mg s.c. day 2
CT, chemotherapy; PFS, progression-free survival; RX, radiological; CBR, clinical benefice rate; LMS, leiomyosarcoma; PFS inv, investigator-assessed PFS; ST-LMS, soft tissue leiomyosarcoma; Ut-LMS, Uterine leiomyosarcoma
Source: Pautier P, et al. ESMO 2021 LBA59

LMS-04: PFS BY BICR, ITT POPULATION

Progression-free survival



	Doxo N=76	Doxo + Trab N=74
Events, n (%)	74 (97%)	65 (88%)
Median PFS, months	6.2	12.2

HR 0.41
95% CI 0.29-0.58; P<0.0001

Conclusion:

- Safety profile of doxorubicin + trabectedin = consistent and manageable toxicity
- Doxorubicin + Trabectedin should be a new standard of care for 1L treatment of metastatic LMS

1L, first-line; BICR, blinded independent central review; CI, confidence interval; Doxo, doxorubicin; HR, hazard ratio; ITT, intent to treat; LMS, leiomyosarcoma; PFS, progression-free survival; Trab, trabectedin
Median follow-up was 37 months
Source: Pautier P, et al. ESMO 2021 LBA59

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Sarcoma: Histology-agnostic approach

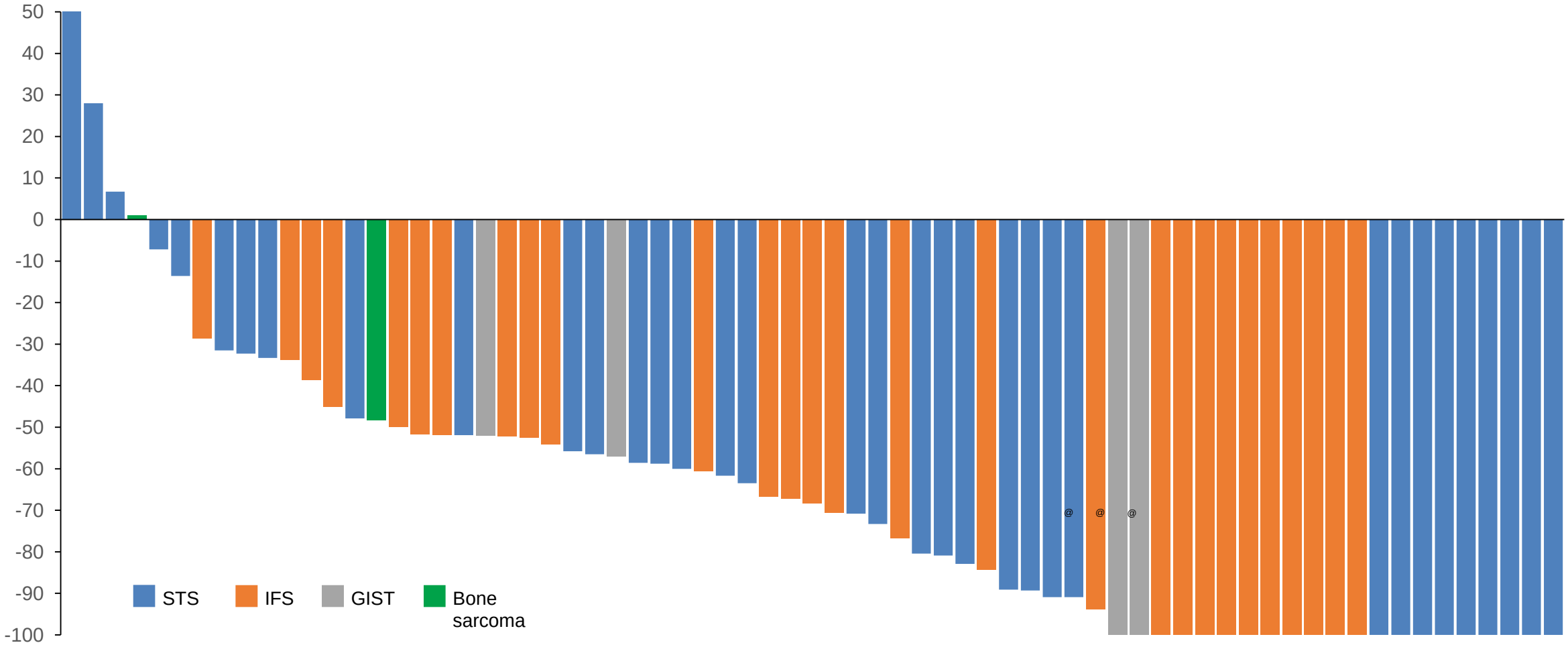
- NTRK-rearranged sarcoma
- Other targetable alterations

Sarcomas with NTRK-fusion

- >90% of infantile fibrosarcoma
- Less than 1% of unselected sarcoma
- Some pathological features
  - Lipofibromatosis
  - fibrosarcoma,
  - and malignant peripheral nerve sheath tumors
- Immunohistochemistry
  - Coexpression of CD34 and PS100 ?
  - IHC NTRK ?

Demetri et al. Ann Oncol 2020;31(11):1506

Efficacy of Larotrectinib in Sarcomas harbouring TRK fusions

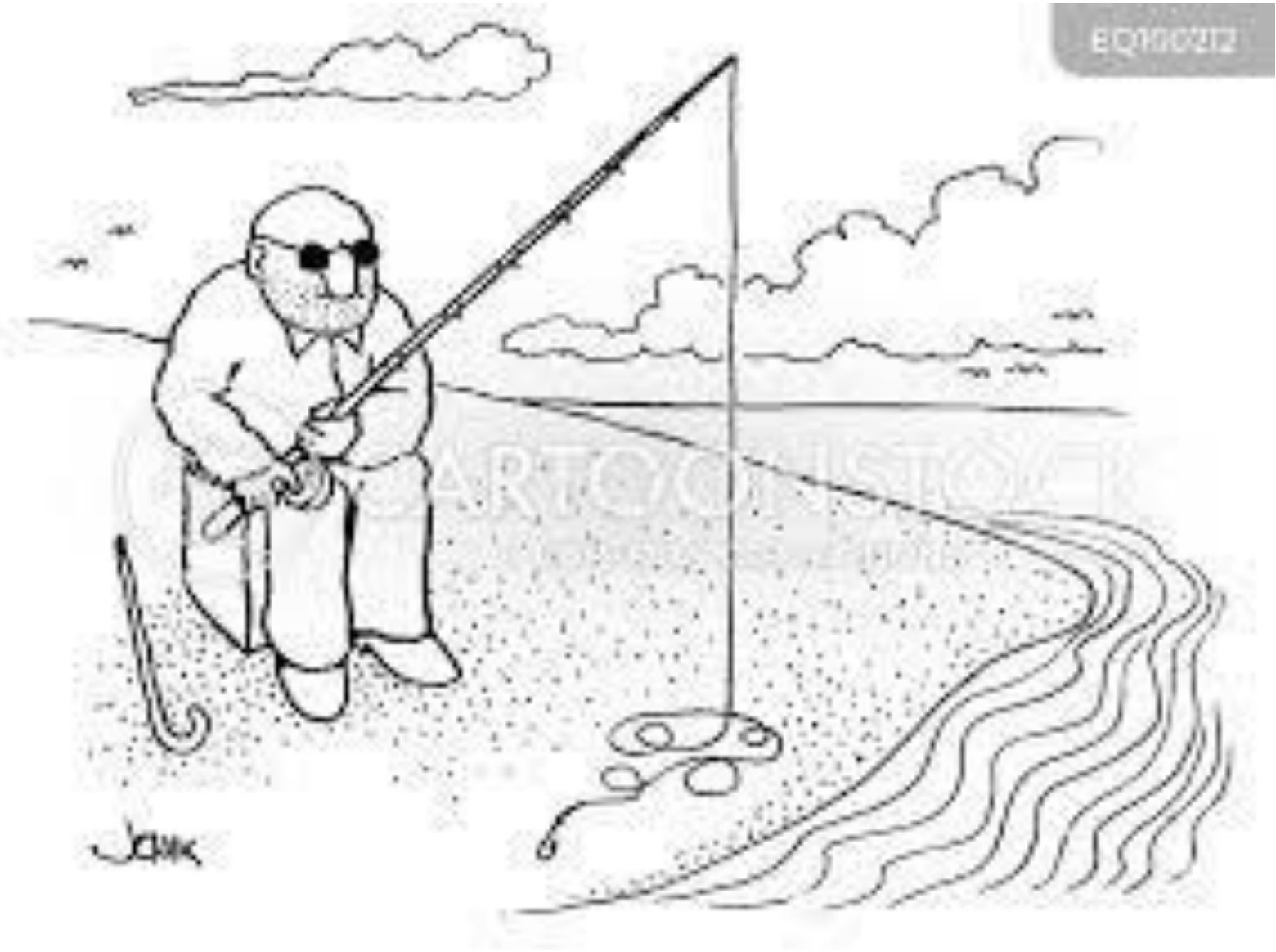


Larotrectenib, entrectenib and sarcoma

	Larotrectenib	Entrectenib
n	71	13
ORR%	87	46
PFS	28	11
OS	44	17

Demetri et al. Ann Oncol 2020;31(11):1506

Extensive screening – the fishing expedition



Screening in unselected sarcomas

Targets	Frequency	Drugs (examples)
RET fusion	Exceptional	selpercatinib

4 to 5% of unselected sarcomas are associated targetable molecular alterations

Gounder et al. ASCO 2019

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- **Immunotherapies**

Immune checkpoint inhibitor

- Response rate to ICI in unselected sarcomas: 2%

- So, 2 main questions
  - Recognize ICI-sensitive Sarcoma
  - Stimulate immune cells in cold tumor
    - Ongoing trials with
    - Combo Radiotherapy and ICI
    - Combo TKI and ICI ….

Toulemonde et al. JAMA Oncol. 2018 Jan 1;4(1):93-97

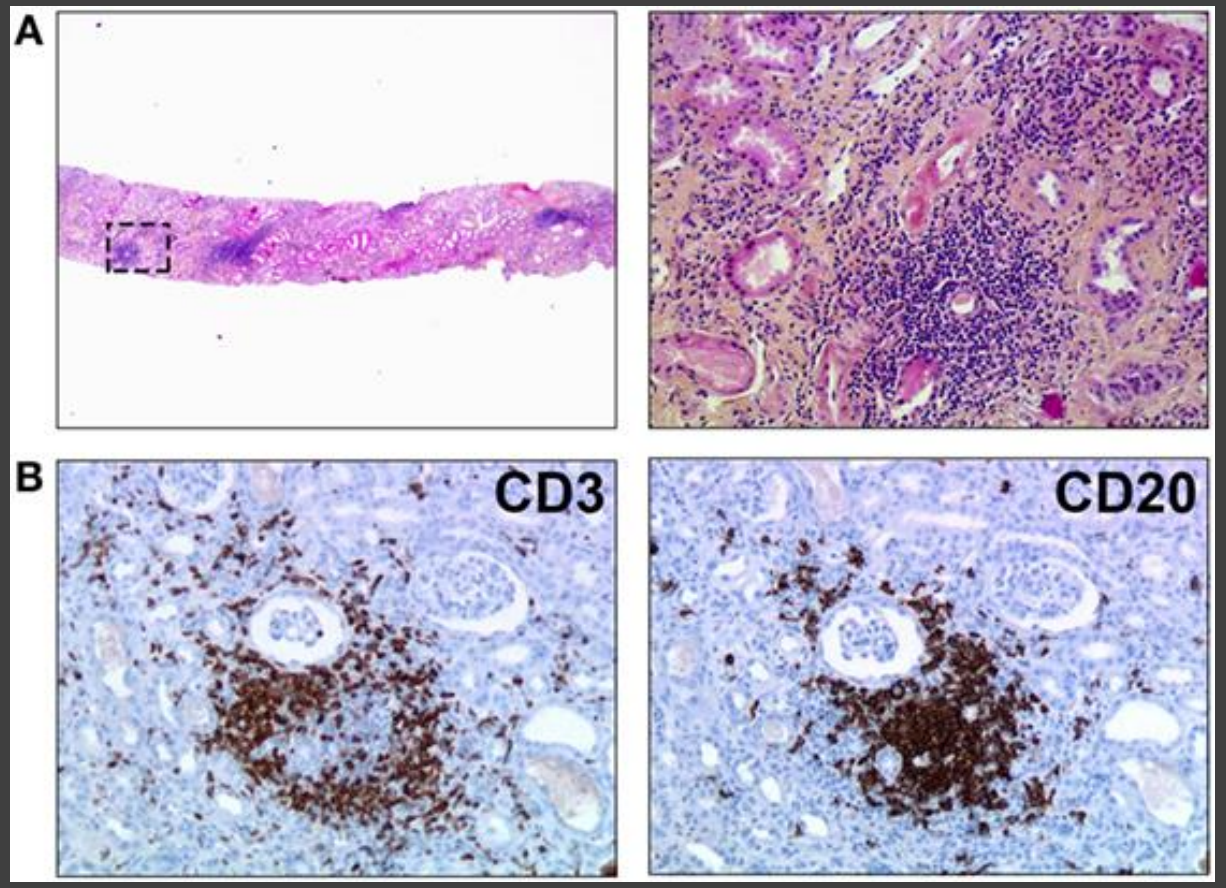
ACSE Pembrolizumab (Blay et al. ESMO 2020)

Histological subtypes	ORR	ORR%
Alveolar soft part sarcoma	5/14	35%
SMARCA4-malignant rhabdoid tumor	2/6	33%
Epithelioid sarcoma	1/5	20%
Chordoma	2/24	8%

MSI-high Sarcoma

- Lam *et al*. Histopathology 2021, 79, 509–520
  - Radiation-induced sarcoma: 1/14 (7%)
  - LMS: 4/88 (5%)
  - Non-alveolar RMS: 2/17 (11%)
- Keynote-158 Cohort K (Pembrolizumab)
  - 351 non-colorectal MSI-high tumor
  - ORR: 31%
  - Includes 14 sarcoma patients (4%)

Tertiary lymphoid structure



- PEMBROSARC Trial
- TLS in 48 out of 240 pts (20%)
- 30 TLS-positive sarcoma
  - ORR: 9/30 (30%)
  - 6month PFR: 40%
  - PFS:4.1 months
  - OS: 18 months

Italiano *et al*.ASCO 2021

Sarcoma and response to ICI

Sarcomas	ORR
Unselected – all comers	≈ 2%
Alveolar soft part sarcoma	≈ 33%
SMARCA4-malignant rhabdoid tumor	≈ 33%
Epithelioid sarcoma	≈ 20% ?
Chordoma	≈ 10%
MSI-high Sarcoma	≈ 30%
TLS-positive sarcoma	≈ 30%

Targeting tumor antigens

- Some antigens are express in some subtypes
  - NY-ESO-1 in 80% of synovial sarcoma (PRAME 90%, MAGE-A4 80%)
  - NY-ESO-1 in 80% of myxoid liposarcoma

- Cell therapies (T-cell receptor)
- Drug-conjugated antibodies (not covered today)

TCR-therapy in Synovial sarcoma

Auth	Therapy	Target	Response
Butle			
Robb			
D'An			
Ram			
Hong et al	ADP-A2M4	MAGE-A4	In cohort 3 (N=28) all seven PR were from SS patients
Morgan et al	TCR (unnamed)	MAGE-A3	Only 1 SS patient. Patient experienced PR.

Response rate 43%

Study Design

1 Screening

Enrollment

4 Lymphodepletion

Day -7 -6 -5

Flu 30 mg/m²/day

Cy 600 mg/m²/day

6 Monitor for toxicity

0

3 Manufacturing

5 SPEAR T-Cell Infusion

7 **Disease Assessments**

MRI/CT scans performed

- Baseline
- Weeks 4, 8, 12, 24, and every 3 months until disease progression

2 **Apheresis/ cell collection**

Positive selection of T-cells (CD3/CD28 Dynabeads)

Lentiviral gene transfer of affinity enhanced TCR

Expansion of T-cells (CD3/CD28 Dynabeads)

Take-home messages

- More than 150 histological subtypes
- First make sure of diagnosis

- New treatments
  - Ripretinib as 4th line in advanced GIST and Avapritinib for D842V-mut GIST
  - Pexidartinib for diffuse-type tenosynovial tumor
  - Tazemetostat in INI1-deficient epithelioid sarcoma
  - Doxorubicin and Trabectedin as 1st-line treatment in LMS

Take-home messages

- 2-4% of sarcoma harboring DNA Damage Repair gene alterations
- 1% of sarcoma harbouring NTRK-fusion and are sensitive to larotrectenib
- Less than 1% of sarcoma harbour ALK, B-Raf, RET or FGFR-fusions

Take-home messages

- Unselected sarcoma are sensitive to ICI in 2% of cases
- Selected Sarcoma are sensitive to ICI in 30% of cases
  - SMARCA4-malignant rhabdoid tumor
  - Alveolar soft part sarcoma
  - MSI-High Sarcoma
  - TLS-positive sarcoma

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Thank to Pr Jean-Yves BLAY